

Emerging Pollutants

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Origin, Structure and Properties

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Library of Congress Card No.: applied for

British Library Cataloguing-in-Publication Data

A catalogue record for this book is available from the British Library.

Bibliographic information published by the Deutsche Nationalbibliothek

The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the Internet at <<http://dnb.d-nb.de>>.

© 2018 Wiley-VCH Verlag GmbH & Co. KGaA, Boschstr. 12, 69469 Weinheim, Germany

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Print ISBN: 978-3-527-33876-4

ePDF ISBN: 978-3-527-69123-4

ePub ISBN: 978-3-527-69121-0

Mobi ISBN: 978-3-527-69122-7

oBook ISBN: 978-3-527-69120-3

Cover Design Wiley

Typesetting SPi Global, Chennai, India

Printing and Binding

Printed on acid-free paper

10 9 8 7 6 5 4 3 2 1

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Epigraph

All substances are poisons; there is none which is not a poison. The right dose differentiates a poison and a remedy.

This early observation concerning the toxicity of chemicals was made by Paracelsus (1493–1541) and it serves as a good starting point for the discussion on micropollutants.

Abbreviations

α -E2	17 α -estradiol
2,3,7,8-TCDD	2,3,7,8-tetrachlorodibenzo- <i>p</i> -dioxin
4-NP	4-nonylphenol
4-OP	4- <i>t</i> -octylphenol
610P	di-(<i>n</i> -hexyl, <i>n</i> -octyl, <i>n</i> -decyl) phthalate
AB	antibiotic
ABS	acrylonitrile butadiene styrene
ACR	acute to chronic ratio
ADI	acceptable daily intake
AEO	alcohol ethoxylate
AOP	advanced oxidation process
APEO	alkylphenol ethoxylate
API	active pharmaceutical ingredient
ATS	amphetamine-type substance
AV	acute (toxicity) value
AWQC	ambient water quality criteria
BBP	butyl benzyl phthalate
BDE	brominated diphenylether
BFR	brominated flame retardant
BHA	butylated hydroxyanisole
BHT	butylated hydroxytoluene
BOD	biochemical oxygen demand
BOP	butyl 2-ethylhexyl phthalate
BPA	bisphenol A
BPF	bisphenol F
BSTFA	<i>N,O</i> -bis-(trimethylsilyl)-trifluoroacetamide
BTBPE	1,2-bis(2,4,6-tribromophenoxy)ethane
BW	body weight
CBZ	carbamezapene
CCC	criterion continuous concentration
CDC	center of disease control and prevention
CEC	contaminants of emerging concern
CI	chemical ionization
CMC	criterion maximum concentration
CNT	carbon nanotube

COD	chemical oxygen demand
CV	chronic (toxicity) value
CWA	Clean Water Act
D711P	di-(heptyl, nonyl, undecyl) phthalate
DAP	diallyl phthalate
DBDPE	decabromodiphenyl ethane
DBP	disinfection by-product
DDT	1,1,1-trichloro-2,2-bis(<i>p</i> -chlorophenyl)ethane
DEET	<i>N,N</i> -dimethyl- <i>m</i> -toluamide
DEHP	di-2-ethylhexyl phthalate
DEP	diethyl phthalate
DES	diethylstilbestrol
DHP	di- <i>iso</i> -hexyl phthalate
DIBP	di- <i>iso</i> -butyl phthalate
DIDP	di- <i>iso</i> -decyl phthalate
DINP	di- <i>iso</i> -nonyl phthalate
DIOP	di- <i>iso</i> -octyl phthalate
DLLME	dispersive liquid-liquid microextraction
DMP	dimethyl phthalate
DnBP	di- <i>n</i> -butyl phthalate
DnHP	di- <i>n</i> -hexyl phthalate
DnOP	di- <i>n</i> -octyl phthalate
DOC	dissolved organic carbon
DPP	di- <i>n</i> -propyl phthalate
DTDP	ditridecyl phthalate
DUP	diundecyl phthalate
DWEL	drinking-water equivalent level
DWT	drinking-water treatment
DWTP	drinking-water treatment plant
E1	estrone
E2	17 β -estradiol
E3	estriol
ECHA	European Chemicals Agency
EDA	effect-directed analysis
EDC	endocrine disrupting chemical
EDDP	2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine
EDSS	environmental decision support system
EDTA	ethylenediaminetetraacetic acid
EE2	17 α -ethynylestradiol
EFSA	European Food Safety Authority
ELISA	enzyme linked immuno sorbent assay
ELS	early life-stage (toxicity test)
ENM	engineered nanomaterial
EP	emerging pollutant
EPA	Environmental Protection Agency
ESI	electrospray ionization
EU	European Union

FACR	final acute to chronic ratio
FAO	food and agriculture organization of the United Nations
FAV	final acute value
FDA	food and drugs administration
GAC	granular activated carbon
GC-MS/MS	tandem gas chromatography-mass spectrometry/mass spectrometry
GC/MS	gas chromatography/mass spectrometry
GC	gas chromatography
GMAV	genus mean acute value
GMCV	genus mean chronic value
HAA	haloacetic acid
HAN	haloacetonitrile
HBB	hexabromobenzene
HBCDD	hexabromocyclododecane
HBRC	hawke's bay regional council
HHCB	galaxolide
HLB	hydrophilic-lipophilic balance
HPG	hypothalamic-pituitary-gonadal (axis)
HPLC	high-performance liquid chromatography
HPT	hypothalamic-pituitary-thyroid (axis)
HRMS	high-resolution mass spectrometry
HTLC	high-temperature liquid chromatography
ID	illicit drug
iodo-THMs	iodo-trihalomethane
IR	infrared
IUPAC	International Union of Pure and Applied Chemistry
JECFA	joint FAO/WHO expert committee on food additives
LAS	linear alkylbenzene sulfonate
LAU	large animal unit
LC-MS/MS	tandem liquid chromatography mass spectrometry/mass spectrometry
LC/MS	liquid chromatography/mass spectrometry
LC	liquid chromatography
LIT	linear ion trap
LLE	liquid-liquid extraction
LOAEL	lowest-observed-adverse-effect level
LOD	limits of detection
LOEC	lowest observed effect concentration
LOQ	limits of quantification
MAE	microwave-assisted extraction
MAR	managed aquifer recharge
MAV	minimum acceptable value
MDMA	3,4-methylenedioxymethamphetamine
MDR	minimum data requirement
MF	microfiltration
MfE	ministry for the environment

MIW SIG	micropollutants in water special interest group
MOA	mode of action
MOE	margin of exposure
MP	microplastic
MS	mass spectrometry
MS/MS	tandem mass spectrometry
MSPD	matrix solid-phase dispersion
MTBE	methyl <i>tert</i> -butyl ether
MTD	minimum therapeutic dose
NBBSA	<i>N</i> -butylbenzenesulfonamide
ND	not detected
NDMA	<i>N</i> -nitrosodimethylamine
NER	non-extractable residue
NF	nanofiltration
NM	nanomaterial
NMR	nuclear magnetic resonance
NOAEL	no-observed-adverse-effect level
NOEC	no-observed-effect concentration
NOM	natural organic matter (present in mg L ⁻¹ level)
NP	nanoparticle
NPEO	nonylphenol ethoxylate
NPE1	nonylphenol monoethoxylate
NPE2	nonylphenol diethoxylate
NSAID	non-steroidal anti-inflammatory drug
OECD	organization for economic development and cooperation
OPE	octylphenol ethoxylate
OPPT	Office for Pollution Prevention and Toxics
P2P	phenyl-2-propanone
PAH	polycyclic aromatic hydrocarbon
PBB	polybrominated biphenyl
PBDE	polybrominated diphenyl ether
PBT	persistent, bioaccumulative and toxic
PC	pharmaceutical
PCA	polychloro- <i>n</i> -alkane
PCB	polychlorinated biphenyl
PCE	tetrachloroethene
PCP	personal care product
PEG	polyethylene glycol
PET	polyethylene terephthalate
PFAS	perfluorinated alkyl substance
PFC	perfluorinated compound
PFCA	perfluorocarboxylic acid
PFOA	perfluorooctanoic acid
PFOS	perfluorooctane sulfonate
PFR	phosphorus flame retardants
PFSA	perfluorosulfonate acid
PM	particulate matter

PNEC	predicted no effect concentration
PoD	point of departure
POP	persistent organic pollutant
PPG	polypropylene glycol
PUB	public utilities board (Singapore)
PVC	polyvinyl chloride
REACH	registration, evaluation, authorisation and restriction of chemical substances
RMA	resource management act
RO	reverse osmosis
SAICM	strategic approach to international chemicals management
SBE	sewage-based epidemiology
SDME	single-drop microextraction
SDWA	Safe Drinking Water Act
SETAC-AU	Australasian society for ecotoxicology
SF	sand filtration
SIM	selected ion monitoring
SMAV	species mean acute value
SOA	secondary organic aerosol
SPE	solid-phase extraction
SPME	solid-phase microextraction
STP	sewage treatment plant
SWCNT	single-walled carbon nanotube
TBBPA	3,3',5,5'-tetrabromobisphenol A
TBEP	tris(2-butoxyethyl) phosphate
TBT	tributyltin
TCE	trichloroethene
TCEP	tris(2-chloroethyl) phosphate
TCPP	tris(chloropropyl) phosphate
TCS	triclosan
TDCPP	tris(1,3-dichloroisopropyl)phosphate
TDI	tolerable daily intake
TEF	toxic equivalency factor
TEP	triethyl phosphate
THM	trihalomethane
TLC	thin-layer chromatography
TMS	trimethylsilyl
TNT	trinitrotoluene
TOF	time-of-flight
TP	transformation product
UF	ultrafiltration
UHPLC	ultra-HPLC
UNEP	United Nations Environment Programme
UPLC	ultraperformance liquid chromatography
U.S.	United States
USEPA	United States Environmental Protection Agency
USGS	U.S. Geological Survey

UV	ultraviolet
VOC	volatile organic compound
VTG	vitellogenin
WHO	World Health Organization
WQC	water quality criteria
WSH	water, sanitation, hygiene and health unit (WHO)
WW	wet weight
WWTP	wastewater treatment plant

Glossary

aerosol colloid of fine particles of solid or liquid droplets suspended in a gas.

alkaloid group of naturally occurring chemical compounds

nitrogen-containing bases. Many of them produce physiological effects on humans and other animals.

antibiotics medications that fight bacterial infections, inhibiting or stopping bacterial growth.

antimicrobials biochemicals that kill or inhibit the growth of microorganisms including bacteria and fungi.

biochemical oxygen demand a measurement of the amount of dissolved oxygen using aerobic microorganisms.

biocide chemical substance or microorganism intended to destroy, deter, and render harmless, or exert a controlling effect on any harmful organism by chemical or biological means.

biodegradation transformation of materials or molecules by bacteria, fungi, or other biological means.

biofiltration filtration technique using a bioreactor containing living material to remove pollutants by biological degradation.

biomarker is a measurable indicator of some biological state or condition. The term is also occasionally used to refer to a substance the presence of which indicates the existence of a living organism. They can be related to exposure or to toxic effects of environmental chemicals.

bioreactor any manufactured or engineered device or system that contains living organisms such as bacteria or yeast.

biosolid organic wastewater solids recovered from a sewage treatment that can be reused after suitable sewage sludge treatment.

contaminant any physical, chemical, biological, or radiological substance or matter with an adverse effect on air, water, and soil.

corrosion chemical reaction between refined metals and the surrounding environment, which converts them into a more chemically stable form, such as oxides, hydroxides, or sulfides and leads to their deterioration.

depressant drug chemical compound that lowers neurotransmission levels, which is to depress or reduce arousal or stimulation in the brain.

detergent metabolites chemical compounds formed when detergents are broken down by wastewater treatment or environmental degradation.

diffuse pollution pollution that may be produced from widespread activities with no single discrete source.

disinfectants a chemical agent used on non-living surfaces to destroy, neutralize, or inhibit the growth of disease-causing microorganisms.

disinfection by-products chemical substances resulting from the interaction of organic matter in water with disinfection agents such as chlorine.

ecotoxicity ability of a chemical or physical agent to affect ecosystems.

effluent wastewater, treated or untreated, that flows out of a treatment plant, sewer, or industrial point source, such as a pipe. Generally refers to wastes discharged into surface waters.

endocrine disruptor molecule that interferes with the endocrine system of living organisms and produces adverse developmental, reproductive, neurological, and immune effects.

ergotism the effect of long-term ergot poisoning, traditionally due to the ingestion of the ergot alkaloids produced by the *Claviceps purpurea* fungus that infects rye and other cereals.

estrogenic compounds natural or synthetic chemicals that can elicit an estrogenic response.

eutrophication nutrient enrichment in bodies of water.

flame retardant chemical added to several manufactured materials, which is able to inhibit or delay the spread of fire by suppressing the reactions produced in the flame or by forming a protective layer on the surface of the treated material.

fragrances chemical substances that impart a sweet or pleasant odor.

global distillation mechanism for transportation of persistent organic pollutants from warmer to colder regions by successive evaporation–deposition processes.

hepatotoxicity damage of the liver parenchyma.

immission effect of pollutants. The term “immission” means to send in. It denotes the external impact on something.

InChIKey the IUPAC International Chemical Identifier is a unique text code assigned to a chemical substance, designed to facilitate searches in databases and the web.

insect repellents chemical substances applied to skin or other surfaces to discourage insects from coming into contact with the surface.

LD₅₀ dose of a substance, in mg kg^{−1}, with a lethal effect on half the test animals to whom it is fed.

liquid–liquid extraction separation process based on the different distribution of the components of a mixture between two immiscible liquid phases.

manure organic matter, principally derived from excrement of animals except in the case of green manure. They are used as organic fertilizer in agriculture.

metabolites products and intermediates of metabolism, produced when the body breaks drugs down. Traces of drugs consumed will end up in the sewer network either unchanged or as a mixture of metabolites. The term metabolite is usually restricted to small molecules.

microfiltration membrane filtration process that uses membranes with pore sizes from 0.1–10 micrometers.

musk term derived from the Sanskrit word “muska-s,” which means “testicle,” and refers to the fragrant of the apocrine glands of the male musk deer (*Moschus moschiferus*).

nanofiltration membrane filtration process that uses membranes with pore sizes from 1–10 nanometers.

nanomaterial materials where a single unit is sized in one, two, or three dimensions from 1–1,000 nanometers.

nanotechnology study and application of extremely small size materials applicable in fields, such as chemistry, biology, physics, medicine, materials science, and engineering.

no observed effect concentration the highest tested concentration of an effluent or a toxicant at which no adverse effects are observed on the aquatic test organisms at a specific time of observation.

nonylphenols are classified within the organic compounds called alkylphenols. They are used in manufacturing surfactants, detergents, emulsifiers, solubilizers, pesticides, antioxidants, and lubricating oil additives.

organophosphorous compound organic molecule containing phosphorous.

persistent organic compound compound resistant to environmental degradation that adversely affects human health and the environment, and can accumulate and pass from species through the food chain.

pesticide generic term for all plant-protection chemicals and biocides.

population all individuals of a type within a specific area, which can be crossed among each other and therefore have a common genetic complement.

pharmaceuticals chemical substances used in the prevention or treatment of physiological conditions.

plasticizer chemical additives that increase the plasticity or fluidity of a material.

pollutant any substance or energy introduced into the environment that produces undesired toxic effects.

poly aromatic hydrocarbons (PAHs) a large group of chemical substances usually found in the environment as a result of incomplete burning of carbon-containing materials such as fossil fuels, wood, and garbage.

priority pollutant regulate chemical pollutant.

reproductive hormones a group of chemical substances, usually steroids, whose purpose is to stimulate certain reproductive functions.

semipermeable membrane biological or synthetic membrane that allows certain molecules or ions to pass through it by diffusion.

size exclusion chromatography a mixture of molecules in solution are separated by their size, and in some cases molecular weight through a gel.

solid-phase extraction sample preparation procedure in which analytes are dissolved or suspended in a liquid phase and separated from other compounds using solid supports, usually contained in a cartridge-type device.

solvents chemical solutions, other than water, capable of dissolving another substance.

steroids a large group of fat-soluble organic compounds with a characteristic molecular structure, which includes many natural and synthetic hormones.

stimulant drugs substances that temporarily increase alertness and energy in living organisms.

surfactant chemical substance that lowers the surface tension between two liquids or between a liquid and a solid.

sweetener natural or synthetic compounds that taste sweet.

teratogenic triggering deformities.

toxin is a poisonous substance produced within living cells or organisms; synthetic toxic substances created by artificial processes are thus excluded.

ultrafiltration filtration through a semipermeable membrane forced by pressure or concentration gradients.

volatile organic compound organic molecule with a high vapor pressure and a great tendency to evaporate.

xenobiotics artificially manufactured substances, foreign matter in the biosphere.

Preface

The so-called contaminants of emerging concern, CECs, are defined as a group of substances, mostly organic compounds, that have been detected in water, soil, and air in very small concentrations, but are not yet subjected to restrictions of any kind. Despite the lack of any current regulation, special concerns have grown around them because of their potential effects on ecosystems and living organisms upon long-term exposition. Most of these compounds have been undetectable with conventional analytic tests for many years, but the development of more sensitive procedures has helped identifying them in water bodies, soils, and even fluids and tissues of vegetables and animals. Many of them remain in the environment after conventional waste treatment, as it happens in waste urban waters. Their chemical structure is of diverse origin, in many cases being related to common human activities such as personal hygiene, agriculture, livestock, and use of medical and pharmaceutical products, household or industrial goods, among others.

Terms such as constituents of CECs, microconstituents, trace organic pollutants, and other similar terminologies are often used in the literature for these classes of chemicals, which are here to stay and require proper attention. Our aim with this book is to describe the main families of such compounds, their characteristics, origin, fate, and detection methods and the state of the art related to emerging pollutants.

Granada, April 2017

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Acknowledgment

Finally, we would like to give our special thanks to Dr Francisco J. Martín Martínez for his revision of part of this work, to Mr David Nesbitt for his invaluable work on the revision of the English version of the manuscript, and to Mrs Laura Bustos-Sánchez for creating the front cover photo.

Introduction

1.1 Chemistry and Development

World War II was one of the most destructive periods of modern history for humanity, but also one of the most inventive periods for the design and production of new chemicals. It was an epoch of such unprecedented innovation that this period has been often referred to as a second chemical revolution. That golden age for chemistry has had, for better or for worse, an undeniable influence in our lives and in the development of civilization. Food production, medicine, pharmacology, and defense underwent unprecedented expansion during those years of scientific and technological advances, and these developments are profoundly influential even today. Regardless of the origin and the underlying reasons for such scientific progress, this historical era supported the development of new chemicals and materials that have improved human welfare in terms of health, longevity, and general living conditions both at the global as well as individual scale. This, however, has also imposed an underestimated burden.

During the first half of the twentieth century, the continuous expansion of the chemical industry and the use of chemicals in many aspects of our life contributed toward creating a positive image of chemistry in our society. Things changed, however, during the 1960s, when two widely sold books began to generate a different kind of social awareness of chemistry and chemical compounds. *Silent Spring* [1], focused on the undesirable effects of the indiscriminate use of pesticides on the environment and *Our Stolen Future* [2] sought to explain how certain chemicals interact with hormones in humans and wildlife. These two works succeeded in providing a new perspective of chemistry among the populace. The ideas presented in these books, together with information on a series of environmental disasters over the following decades, caused by bad practices in the use and handling of chemicals in certain chemical industries and also by unsafe factory design, cast a dark shadow over everything related to chemistry and chemicals. Examples of severe episodes of pollution are the Seveso (Italy) disaster caused by the 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD) leak in 1976, the Love Canal evacuations in Niagara (New York) caused by the spill of 21,000 t of toxic waste that was buried underground by a local company from the 1940s until 1978,

and the Union Carbide leak in Bhopal (India) in 1984, when around half a million people were exposed to methyl isocyanate gas and other substances, and many of them died, which is considered the worst disaster in the chemical industry ever.

All these contributed to an enormous loss of prestige and increased societal concerns about anything related to chemistry throughout the second part of the twentieth century. Despite the many benefits that chemistry has provided for our lives, not to mention that chemistry itself is at the origin of life and existence, the words “chemistry” or “chemical” has taken on a negative connotation in recent times.

Things have begun to change back again in recent decades. Our awareness of the need to preserve the environment for generations to come has risen greatly in the last few years, and is reflected in public opinion, international organizations, governments and, of course, chemists. Profuse legislation has been issued worldwide to set the acceptable levels of pollutants in water, air, or soil, while strong control mechanisms have been implemented to protect the environment and human health. More specific to the chemical industry, numerous documents and institutional publications indicate increasing concerns about bad practices that are prevalent in the production and use of hazardous chemicals. In 1988, the United Nations Environment Programme prompted the signing of the “International declaration on a cleaner production,” which remains applicable today. In this programme, a comprehensive preventive strategy was developed to describe processes, products, and services in the interest of health and safety as well as social and environmental welfare. Concepts such as eco-efficiency, ecological productivity, and pollution prevention were introduced at that time to establish the practices that we apply today. Also, new contributions arising from industry, driven by the World Business Council for Sustainable Development, are remarkable. This international organization formed by more than 125 large companies in 35 countries, and 20 related industries is grouped around three concepts: economic growth, ecological balance, and social development; it has become a forum since 1990, which promotes sustainable development in the world industry.

In 1990, the USEPA, through a document called the Pollution Prevention Act, which establishes US policies to “prevent or reduce pollution on any occasion possible,” an office within the Environmental Protection Agency (EPA), Office for Pollution Prevention and Toxics (OPPT), has promoted the preparation and production of new chemicals that are less hazardous to human health and the environment. The goal set is to replace dangerous substances used in industry as well as to improve existing methods of production, to minimize environmental impact. On this basis, a specific project called Design for the Environment, to address “alternative synthetic pathways for pollution prevention,” has been developed. This program is actually considered the seed of Green Chemistry. Simultaneously, the Clinton administration launched the “Presidential Green Chemistry Challenge” together with the EPA’s design for the environment and the scientific community. Since 1996, five annual prizes are awarded focusing on the following priority areas of chemistry: alternative synthetic pathways and reaction conditions and the design of safer chemicals. This contest has helped to

improve more sustainable methods and procedures in chemistry, especially for industry, to synthesize safer chemicals and to gain a deeper understanding and complete knowledge of the impact of synthetic compounds on the environment. It is now clear that the uses and the benefits of chemicals, either known or new, must be accompanied by extensive investigation of possible hazards these chemicals may present, as well as an evaluation of the environmental risks related to their production, transport, and handling, and the implementation of an efficient communication policy.

The chemical industry plays an essential role in today's economy in developed countries, being considered a strategic sector, and contributing significantly to the gross domestic product. For example, the chemical industry is the largest manufacturing sector in the United States and the second largest in Europe and Japan, accounting for approximately 5% of the gross domestic product in each of these countries. This represents more than \$1.6 trillion of the total market and has provided employment to over 10 million people globally.

1.2 Pollution and Contamination

Pollution is the process of dirtying land, water, air, or other parts of the environment, or making them inappropriate places for use. The process is complex, driven by the introduction of undesirable substances, pathogens, or energy that disturbs both the environment's natural status and the development of specific areas. There are three main groups that contribute to pollution, namely: chemical, physical, and microbiological. Sometimes, the term "contamination" is used as well. Although in most cases, this can be considered a synonym, confusion may arise because of elusive differences of degree. In 2007, Chapman [3] proposed a clarification in this regard:

Contamination is simply the presence of a substance where it should not be or at concentrations above background. Pollution is contamination that results in, or can result in, adverse biological effects to resident communities. All pollutants are contaminants, but not all contaminants are pollutants.

On the other hand, "emissions" is the term used to describe contaminants that are released into the environment or emitted by various sources. There are many sources of emissions: natural and anthropogenic.

Natural sources include biogenic emissions that are caused by living organisms and interaction of water bodies or the atmosphere with soil, rocks, or sediments. During the course of the earth's history, the composition and the average of the compounds present in the diverse spheres have been changing either by natural procedures or by human activities. Accepted data comparing emissions of gases of natural and human origin are listed in Table 1.1

Sources of contamination from human activities (anthropogenic) are diverse. They include emissions from sources such as transport, industry and factories, agriculture livestock, or household activities.

Table 1.1 Example of emissions of natural and human origin.^{a)}

Emission	Natural (million t yr ⁻¹)	Human (million t yr ⁻¹)	Emission	Natural (million t yr ⁻¹)	Human (million t yr ⁻¹)
CO ₂	600,000	22,000	NH ₃	1200	7
CO	3800	550	NO ₂	770	53
Hydrocarbons	2600	90	N ₂ O	145	4
CH ₄	1600	110	SO ₂	20	150

a) Data taken from Ref. [4].

1.3 Chemical Pollutants

Chemical pollutants are organic or inorganic compounds that can harm the environment. They can be substances that are directly emitted to the environment by different means or substances resulting from chemical or photochemical reactions or metabolic transformations by living organisms. The reactions give rise to primary pollutants, while transformations produce secondary pollutants. The latter are usually more difficult to handle, especially when emitted after being metabolized by a living organism from a former toxic or potentially toxic substance, in which case both the original molecule and the metabolite are considered pollutants.

The number of described organic and inorganic substances to date exceeds 127 million¹ and most are organic compounds. Therefore, it follows that most pollutants are organic molecules. From the environmental chemistry point of view, organic pollutants can be classified as volatile organic compounds (VOCs) and persistent organic pollutants (POPs).

VOCs are molecules with a low number of carbons in their structures (no more than 10 or 12) that have low boiling points, and vapor-pressure values, usually. Therefore, they evaporate readily and their main occurrence is in the atmosphere, but they can also be found in surface waters, ground waters, or soils. Typical examples of such compounds are common organic solvents, such as trihalomethanes or formaldehyde.

POPs are either semi-volatile molecules or molecules with a low volatility that have remarkable toxicity. POPs strongly resist chemical and biological degradation, so they may have a half-life of years or decades in soils or waters and several days in the atmosphere. But there is no consensus on how long the half-life should be in a given media for a compound to be considered “persistent” [5].

Between aquatic media and soils, POPs partition preferably to solids, mainly on soil organic matter, avoiding the aqueous phase and also partition into lipids in living organisms rather than remaining in the aqueous milieu of cells; thus, they may be stored in fatty tissue. This is a consequence of being typically “water-hating” and “fat-loving” because of their hydrophobicity and liposolubility and therefore they are bioaccumulative. On the other hand, they may

¹ Data taken from the Chemical Abstracts Service (February 21, 2017), <http://www.cas.org>.

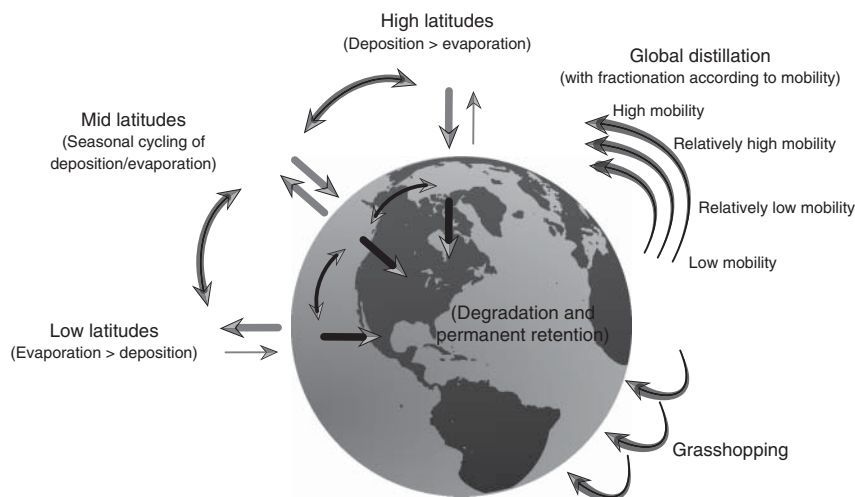


Figure 1.1 POP global migration processes. (Data taken from Ref. [6].)

volatilize partially from soils, vegetation, and water bodies into the atmosphere. This feature, together with their resistance to degradation reactions in air enables them to travel great distances by a mechanism known as global distillation or grasshopper effect, causing a pollutant “jump,” and re-deposit several times from the Ecuador to colder areas. As a result, POPs are able to accumulate in areas far from where they were used or emitted (see Figure 1.1).

Included in this group of POPs are pesticides such as 1,1,1-trichloro-2,2-bis (*p*-chlorophenyl)ethane (DDT) and their metabolites, chlorinated pesticides such as aldrin, toxaphene, other chlorinated molecules such as hexachlorobenzene, polychlorinated biphenyls, and by-products formed in the fabrication of many other chemicals, or in the combustion of fuels or wastes such as dioxins and dibenzofurans. Many POPs are included in the Stockholm convention and are no longer produced or strongly regulated.

According to USEPA, pollutants can be classified into two groups:

- Priority pollutants.
- Emerging pollutants.

EPA’s priority pollutants are a set of regulated chemical substances that have been selected on the basis of their known or suspected carcinogenicity, mutagenicity, teratogenicity, or high acute toxicity, and for which there are well-defined analytical test methods. They have been established in the Clean Water Act (CWA), as a basic structure for regulating discharges of pollutants into US waters, as well as regulating quality standards for surface waters. CWA, first enacted in 1948, was later called the “Federal Water Pollution Control Act.” In 1972, the act was significantly reorganized and expanded to become the currently known CWA.²

² Summary of the Clean Water Act. Accessed April 26, 2017. <http://www2.epa.gov/laws-regulations/summary-clean-water-act>.

Most of these priority pollutants are subject to regulation by rules and laws of individual countries or supranational agencies. This group includes substances such as POP, heavy metals, some pesticides, or polycyclic aromatic hydrocarbons (PAHs). Within this priority category, substances or groups of substances are well known to be toxic, bio-accumulative, and hazardous for the environment. In the European Union (EU), the levels of organic priority pollutants in waters, including some metals (Cd, Ni, Hg, and Pb), are regulated according to the Directive 2008/105/EC [7]. For the United States, the EPA in the CWA references, the list of toxic pollutants includes a set of 126 priority pollutants.

1.4 Pollutants in the Environment

According to the World Health Organization (WHO), more than 100,000 chemicals are released into the global environment every year as a consequence of their production, use, and disposal. The fate of a chemical substance depends on its chemical structure and physicochemical properties, in combination with the characteristics of the environment where it is released.

Pollutants discharged into the environment may be “natural” or “human-made.” A “natural” pollutant is a substance that can appear without human introduction. For example, trace metals can be considered naturally occurring substances and are generally found in the environment only in moderate amounts that do not pose health threats. However, natural pollutants can also have anthropogenic origins. Human activities often cause the release of a large amount of inorganic compounds containing metals into the environment and it is not the mere presence of a contaminant that makes it toxic, but its concentration.

The stability, transport, and transformation of chemical compounds in the environment are consequences of several factors. Some of them depend on the intrinsic nature of the compound, such as chemical stability, vapor pressure, or solubility in water, while others depend on environmental conditions, such as partition-coefficient octanol/water and air/water sorption processes in soils, or bioconcentration. Chemical compounds in the environment can be transformed by chemical, photochemical, or microbiological processes or by a combination of these. The main reactions of chemical compounds in the environment are the following:

- Hydrolysis.
- Acid–base transformations.
- Redox reactions.
- Substitution.
- Elimination.
- Complexation.
- Precipitation.

Metal derivatives undergo chemical transformations that, for example, alter toxicity depending on oxidation state, but they stay in the environment unaltered. However, organic compounds can be transformed or not, depending on the structure. In many cases, a combination of individual processes takes place, giving rise

to simpler molecules that can be degraded by microorganisms. Moreover, other chemical compounds are resistant to degradation and remain almost unchanged in the environment. These are called POPs and can be found in soil, water bodies, and living organisms tissues, because of their bioaccumulation. Smaller organic molecules have a high tendency to be present in the atmosphere because of their high vapor-pressure values, VOCs, but they can also be found in water bodies, absorbed in soil particles or in plants that can be ingested by animals or humans.

1.5 Concept of Emerging Pollutants

Emerging pollutants (EPs) are chemical substances, commonly not regulated, which can be detected in low or very low concentrations by analytical techniques, raising special concern because their long-term adverse effects on the environment and on human health remain unknown. EPs can be defined as compounds of different origin and chemical nature whose presence in the environment, or by consequences of their presence, have gone largely unnoticed and remain unregulated.

International organizations and national agencies of specific countries have developed some definitions of EPs, which illustrate different aspects related to the issue and which can help to understand the dimension of the problem and its consequences.

The network of reference laboratories, research centers, and related organizations for monitoring emerging environmental substances in Europe (NORMAN) is an international project³ funded in 2005 by the European Commission in order to promote the creation of a permanent network among reference laboratories and research centers, in collaboration with the parties involved (industry, standardization bodies, non-governmental organizations, etc.) [8].

According to EU NORMAN network such chemicals are:

Substances that have been detected in the environment, but which are currently not included in routine monitoring programs at the EU level and whose fate, behavior, and (eco)toxicological effects are not well understood. In the United States, the EPA has replaced the expression “EPs” with the abbreviation CEC.⁴ NORMAN has identified a list of the chemicals most frequently considered as emerging substances and EPs.⁵ The substances are selected by a workshop (NORMAN Prioritisation Working Group), based on current citations in the scientific literature, and included in the definition of “emerging substances” and “EPs” given in the NORMAN glossary of terms, which are regularly revised.

3 Network of reference laboratories, research centers and related organizations for monitoring of emerging environmental substances. Accessed February 21, 2017. <http://www.norman-network.net>.

4 Contaminants of Emerging Concern including Pharmaceuticals and Personal Care Products. Accessed April 26, 2017. <http://water.epa.gov/scitech/cec>.

5 (List of Emerging Substances latest update February 2016), <http://www.norman-network.net/?q=node/19>.

According to the U.S. Geological Survey (USGS), CECs are defined as:

Any synthetic or naturally occurring chemical or any microorganism that is not commonly monitored in the environment but has the potential to enter the environment and cause known or suspected adverse ecological and/or human health effects [9].

A representative example of this item can be found in some cases of emerging chemical or microbial contaminants to the environment, which have likely occurred for a long time but have not been recognized for years until the development of new analytic methods.

Because of the presence of CECs in low concentrations, some members of the scientific community have coined the term “micro-pollutants.” These chemical compounds of emerging concern are present in wastewater, soil, ground water, or drinking water in low to very low concentrations (pg L^{-1} to ng L^{-1}) [10].

A remarkable feature of EPs is their continuous production and consumption, and consequently continuous introduction into the environment. Due to the continuous exposure they need not be persistent to cause adverse long-term effects.

According to this, EPs may be new substances, or on the contrary, they may have been long present in the environment but only recently detected. We may just be beginning to understand their effect on the environment or human health, or we may only now have the ability to detect them in the environment [9].

In summary, further research and tests are required. EPs are prospects to be included in regulatory rules for an appropriate control and prevention of pollution.

1.6 Historical Background of Emerging Pollutants

Concern on EP motivates the development of analytical techniques in order to detect chemical compounds in a μg and even pg range of concentrations, especially in water samples. For example, in 2002 USGS published a study that detected the presence of pharmaceuticals, hormones, and other organic compounds in streams all over the United States down to trace levels. This agency considered five new analytical methods by that time, which detected concentrations of 95 organic substances in surface water from samples taken between 1999 and 2000 from 139 streams across 30 US states. Samples showed detectable quantities of organic wastewater contaminants and 82 of the 95 target compounds were found [11].

The study constantly being brought up to date in order to control the measurement of 263 compounds, can be consulted online for different matrices.⁶ The main results of this study can be extrapolated to other areas. According to NORMAN, at least 700 substances, including some metabolites of such substances,

6 USGS: Contaminants of Emerging Concern in the Environment. Accessed April 23, 2017. <http://toxics.usgs.gov/investigations/cec/index.php>. An exhaustive list of published emerging contaminants and the common analytical methods used for determining EPs is also available.

are categorized into several classes, which have been identified in the European aquatic environment [12].

From all the above discussions, EPs may be potentially considered in the next few years as priority substances and subject to regulation. Most of these new pollutants are caused by human activity over the last few decades. They come from several branches of industry and scientific research and are related to lifestyle habits, while some are relatively new, such as a variety of chemicals coming from the appearance of new materials or related to nanotechnology. In other cases, daily household activities have made some household chemicals or pharmaceutical products appear in a massive way. Additionally, feed-production methods use antibiotics, antiseptics, or plaguicides as common products used in the prevention of diseases and elimination of pests in livestock and crops [13].

In some cases, the release of an emerging chemical or microbial contaminant into the environment has likely occurred for a long time but may not have been recognized until the development of new detection methods. In other cases, the synthesis of new chemicals or changes in the use and disposal of existing chemicals can create new sources of emerging contaminants. In other words, CECs are substances that we are beginning to suspect could cause harm. They may be new substances or may have been long used but have only been recently found in the environment. We may just be beginning to understand their effect on the environment and on human health, or we may only now have the ability to detect them in the environment [9].

1.7 Classification of Emerging Pollutants

EPs can be classified in several ways based on their origin, use, potential effects, or environmental fate. Some major groups considered as EPs are summarized as follows:

- Pharmaceutical and veterinary products.
- Disinfectants and biocides.
- Illicit drugs.
- Personal care chemicals and other lifestyle products.
- Industrial chemicals.
- Food additives.
- Water disinfection by-products.
- Nanomaterials.
- Waterborne pathogens.
- Biological toxins.

Other categories describe their nature, such as surfactants that can be used in detergents to aid grease removal and in cosmetics as an emulsifier; or synthetic hormones that mimic the action of natural hormones. Unfortunately, these categories can overlap, leading to some confusion, and there is no standardized set of categories used in the various studies on CECs. Some of the most common terms used to categorize CECs are listed in Table 1.2.

Table 1.2 Representative list of EPs.

Category	Compounds
Veterinary and human antibiotics	Trimethoprim, erythromycin, lincomycin, sulfamethoxazole, ampicillin, azithromycin, doxycycline, amoxicillin
Analgetics, anti-inflammatory drugs	Codeine, ibuprofen, acetaminophen, aspirin, diclofenac, fenoprofen, dipyron metabolites
Psychiatric drugs	Diazepam, carbamazepine, lorazepam, bromazepam
Lipid regulators	Bezafibrate, clofibrac acid, fenofibrac acid, atorvastatin, amlodipine, cilazapril, simvastatin, enalapril
β -Blockers	Metoprolol, propranolol, timolol, bisoprolol
X-ray contrast agents	Iopromide, iothalamic acid, diatrizoic acid,
Steroids & hormones	Estradiol, estrone, estriol, diethylstilbestrol,
Drugs of abuse	Morphine, dihydrocodeine, cocaine
Sun-screen agents, insect repellents	Benzophenone, 3-(4-methylbenzylidene)camphor, <i>N,N</i> -diethyl-3-methyl-benz-amide
Fragrances	Nitro, polycyclic, and macrocyclic musks
Biocides	Triclosan, 2-benzyl-4-chlorophenol
Detergents	2-[2-(4-Nonylphenoxy)ethoxy]ethanol, 2-[2-(4-octylphenoxy)ethoxy]ethanol
Food additives	Sucralose, triacetin
Antioxidants	2,6-Di- <i>tert</i> -butylphenol
Water (disinfection)	2,2,2-Trichloroacetamide, chloroacetaldehyde
Gasoline additives	<i>tert</i> -Butyl methyl ether, dialkyl ethers
Anticorrosives	1 <i>H</i> -Benzotriazole,
Antifoaming agents	2,4,7,9-Tetramethyl-5-decyne-4,7-diol
Antifouling compounds	Organotin (dibutyltin and triphenyltin ions), cybutryne
Plasticisers	Bisphenol A
Wood preservatives	2,4-Dinitrophenol
Flame retardants and impurities	Polybrominated diphenyl ethers (PBDEs), tetrabromobisphenol A, C ₁₀ –C ₁₃ polychlorinated alkanes, tris(2-chloroethyl) phosphate, polybrominated biphenyls (PBBs), polybrominated dibenzo- <i>p</i> -dioxins (PBDDs), polybrominated dibenzofurans (PBDFs), hexabromocyclododecanes (HBCDs)
Perfluorinated compounds	Perfluorooctane sulfonates (PFOS), perfluorooctanoic acid
Siloxanes	Cyclic (hexamethylcyclotrisiloxane, octamethylcyclotetrasiloxane, decamethylcyclopentasiloxane,); linear (octamethyltrisiloxane, decamethyltetrasiloxane, dodecamethylpentasiloxane,)
Algal toxins	Microcystins (microcystin-LR)
Bio-terrorism/sabotage agents	Chloropicrin
Nanoparticles	Limestone (nanoparticles), titanium dioxide (nanoparticles)
Pesticides	Organophosphorus pesticides, thiocarbamates, 2-aminobenzimidazole

1.8 Regulations and Normatives

EPs are by definition compounds that are not subject to regulation. Regulations and controls are focused on traditional pollutants, and different organizations and governmental institutions around the world have normatives and directives to preserve environmental quality, especially related to waters, whether surface or underground waters, which may be potentially used for human consumption. On the other hand, such institutions periodically present rules on different aspects of emerging contaminants (e.g. WHO, food and agriculture organization of the United Nations (FAO), joint FAO/WHO expert committee on food additives (JECFA), USGS, USEPA, Australasian society for ecotoxicology (SETAC-AU), etc.), all paying attention to the substances of special concern because of their potential adverse effects. Therefore, it is possible to find legislation and recommendations at several levels, according to the tested or potential effects of chemical substances.

The European Commission [7] has outlined a legislation covering a broad range of organic and inorganic pollutants over the years. However, the legislation is expected to broaden to encompass a greater number of municipally derived chemicals described as CECs. For example, following the recent proposal, pharmaceuticals 17β -estradiol (E2), 17α -ethynylestradiol (EE2), and diclofenac have been designated as priority hazardous substance. Proposed legislative targets for consent were 0.4, 0.035, and 100 ng L⁻¹ for E2, EE2, and diclofenac, respectively [14].

The EPA identifies contaminants to regulate the drinking water in the United States, and has outlined three levels of EPA-set regulatory limits for the amounts of certain contaminants in water provided by the public-water systems. These contaminant standards are required by the Safe Drinking Water Act (SDWA). The EPA seeks to protect public health by implementing the SDWA provisions while working with governments, agencies, tribes, and many other partners.

The National Primary Drinking Water Regulations (NPDWRs) comprise a set of mandatory water quality standards for drinking-water contaminants based on the concept of “maximum contaminant levels” (MCLs) to protect the population against substances that present a risk to human health. Primary standards and treatment techniques for these substances limit the levels of contaminants in drinking water, such as microorganisms, disinfectants, and a group of inorganic and organic chemicals, including radionuclides.

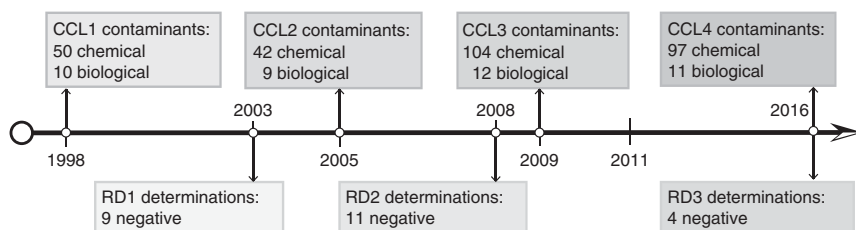


Figure 1.2 Timeline of EPA regulations and lists of contaminants.

Table 1.3 Toxicological guideline values established by EFSA and JECFA.^{a),b)}

Element/species	Year [Reference]	Type	Value
Metals			
Mercury	2011 [15]	PTWI	4 µg kg ⁻¹ (bw week ⁻¹)
	2012 [16]	TWI	4 µg kg ⁻¹ (bw week ⁻¹)
Methylmercury	2003 [17]	PTWI	1.6 µg kg ⁻¹ (bw week ⁻¹)
	2012 [16]	TWI	1.3 µg kg ⁻¹ (bw week ⁻¹)
Lead	2011 [18]	BMDL01	0.50 µg kg ⁻¹ (bw day ⁻¹)
Cadmium	2011 [18]	PTMI	25 µg kg ⁻¹ (bw month ⁻¹)
	2009 [19]	TWI	2.5 µg kg ⁻¹ (bw week ⁻¹)
Arsenic	2011 [15]	BMDL0.5	2–7 µg kg ⁻¹ (bw d ⁻¹)
	2009 [20]	BMDL10	0.3–8 µg kg ⁻¹ (bw d ⁻¹)
Pharmaceuticals and personal care products			
Benzylpenicillin	1990 [21]	ADI	<30 µg kg ⁻¹ bw
Oxytetracycline	2002 [22]	ADI	0–30 µg kg ⁻¹ bw
Enamectin	2013 [23]	ADI	0–0.5 µg kg ⁻¹ bw
Derquantel	2012 [24]	ADI	0–0.3 µg kg ⁻¹ bw
Flumequine	2007 [25]	ADI	0–30 µg kg ⁻¹ bw
Carazolol	1995 [26]	ADI	0–0.1 µg kg ⁻¹ bw
Dexamethasone	2009 [27]	ADI	0–2 µg kg ⁻¹ bw
Tilmicosin	1998 [28]	ADI	0–40 µg kg ⁻¹ bw
Triclabendazole	1993 [29]	ADI	0–3 µg kg ⁻¹ bw
Tylosin	2009 [27]	ADI	0–30 µg kg ⁻¹ bw
Avilamycin	2009 [27]	ADI	0–2 µg kg ⁻¹ bw
Endocrine disruptors			
Bisphenol A (BPA)	2015 [30]	TDI	4 µg kg ⁻¹ bw
E2	2000 [31]	ADI	0–0.05 µg kg ⁻¹ bw
Testosterone	2000 [31]	ADI	0–2 µg kg ⁻¹ bw
Progesterone	2000 [31]	ADI	0–30 µg kg ⁻¹ bw
Melengestrol acetate	2001 [32]	ADI	0–0.03 µg kg ⁻¹ bw
PFOS	2008 [33]	TDI	150 ng kg ⁻¹ (bw d ⁻¹)
PFOA	2008 [33]	TDI	1500 ng kg ⁻¹ (bw d ⁻¹)
Polycyclic aromatic hydrocarbons			
Benzo[<i>a</i>]pyrene	2006 [34]	BMDL10	0.10–0.23 mg kg ⁻¹ (bw d ⁻¹)
	2008 [35]	BMDL10	0.07–0.20 mg kg ⁻¹ (bw d ⁻¹)
Chrysene	2008 [35]	BMDL10	0.17–0.45 mg kg ⁻¹ (bw d ⁻¹)
PAH ^(c)	2008 [35]	BMDL10	0.34–0.93 mg kg ⁻¹ (bw d ⁻¹)
PAH ^(d)	2008 [35]	BMDL10	0.49–1.35 mg kg ⁻¹ (bw d ⁻¹)

Table 1.3 (Continued)

Element/species	Year [Reference]	Type	Value
Brominated flame retardants			
Pentabromodiphenyl ether	2012 [36]	LD ₅₀	2640–6200 mg kg ⁻¹ bw
Polybrominated biphenyls	2010 [37]	LD ₅₀	64–150 mg kg ⁻¹ bw
Hexabromocyclododecane	2011 [38]	NOEL	10 mg kg ⁻¹ bw
Tetrabromobisphenol A	2011 [39]	BMDL10	16 mg kg ⁻¹ bw

- a) Data taken from Ref. [40].
- b) ADI, acceptable daily intake; BMDL, benchmark dose lower limit of the 90% confidence interval; LD, lethal dose; NOEL, no-observed-effect level; PTMI, provisional tolerable monthly intake; PTWI, provisional tolerable weekly intake; TDI, tolerable daily intake; TWI, tolerable weekly intake.
- c) Benzo[*a*]anthracene and benzo[*b*]fluoranthene.
- d) Benzo[*k*]fluoranthene, benzo[*ghi*]perylene, dibenz[*a, h*]anthracene, and indeno[1, 2, 3 – *cd*]pyrene.

The National Secondary Drinking Water Regulations (NSDWRs) comprise guidelines and recommendations for contaminants that are not considered to present a risk to human health. The amount of such substances are quantified as “secondary maximum contaminant levels” (SMCLs) and they represent non-mandatory water quality standards. These contaminants comprise a group of 15 substances that may have an influence on aesthetic considerations, such as taste, color, and fragrances, effects that do not harm the body but are still undesirable such as tooth or skin discoloration or technical effects such as corrosivity and staining related to corrosion, which have remarkable economic implications.

There is a third level that comprises a list of contaminants that are currently not subject to any promulgated regulations, but by virtue of having been detected in public water systems they are listed under the so-called contaminant candidate list (CCL), following a process that was initiated to develop a regulation (regulatory determination, RD) for a specific contaminant in case it has an adverse effect that would lead it to be included under the SDWA regulations. This institution has developed several lists from 1998, (CCL 1, 2, 4, and 4) (see Figure 1.2).⁷

Table 1.3 shows an example of toxicological guideline values established by European Food Safety Authority (EFSA) and JECFA for some EP classes.

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2

Occurrence and Removal of Environmental Pollutants

2.1 Introduction

CECs have become a subject of interest for environmental research because of the potential impact of these chemicals on human health and ecosystems. Scientific papers on the subject have grown notably every year. Most CECs differ from classical environmental pollutants, such as heavy metals or pesticides. CECs are chemicals present in the everyday life of millions of people and can be detected by modern analytical techniques. Although these chemicals have likely been entering the environment for as long as they have been in use, they have gone unnoticed until they were recently noticed in air, water, soil, and biota. The study and research on such substances is necessarily a multidisciplinary matter due to the convergence of several disciplines such as chemistry, chemical engineering, environmental chemistry, biology, biochemistry, environmental sciences and engineering, agricultural engineering, microbiology, molecular biology, and biomedical engineering [1].

2.2 Pollutants in the Atmosphere

Dusts, gases, and water vapor released into the air can have either a direct or an indirect effect on human living conditions and, although no chemical reactions are noticeable, they become significant in conjunction with other air-pollution factors. Dusts and aerosols come from natural as well as anthropogenic sources, although approximately more than half of the total emission of dust and aerosol is of natural origin [2].

It is not possible to define dust chemically. Dust refers to particles of solid substances with $> 1 \mu\text{m}$ diameter; globally, mineral dust dominates by far. Aerosols are colloidally dispersed systems, and, according to the definition of a colloid, the particle diameter lies between 0.1 and $0.001 \mu\text{m}$. Aerosols contain not only solids, but also liquid droplets (ranging in size between 0.1 and $1 \mu\text{m}$), which can also contain dissolved substances.

Natural emission sources include salt grains from seawater spray, mineral dust from dry soil, dust and ash from volcanoes, smoke particles from forest and range,

and dust particles formed in the reaction of gases such as nitrates and sulfates. Anthropogenic emission sources include industrially generated dust and smoke particles, and soot and smoke from incineration plants.

The length of time that particles remain in the atmosphere and their dispersal depend on their size and density. Coarser particles settle within hours or days. In addition, they can also drift over hundreds of kilometers. Particles with a diameter $< 1 \mu\text{m}$, to a large extent, escape being washed out by precipitation, and consequently have residence periods of 10–20 d. For stratospheric dusts and aerosols, residence times of 1–3 yr are likely. The emission of dust changes with the season: naturally occurring dusts attain their maximum during the dry summer months, while the anthropogenic dusts exhibit a significant winter maximum, especially in densely populated regions.

According to toxicology reports, particles of size $< 5 \mu\text{m}$ have a strong tendency to disperse, as in gas. As a result, they are not filtered out by the ciliated epithelia of the bronchial tubes. Therefore, they remain longer in the atmosphere than do dust particles.

The next question is: how much pollution is acceptable? Limits should be established in accordance with an appropriate system of assessment, in which the health of living beings should be accorded priority. However, the limits that are established at any time can only be viewed as temporary guidelines. They will have to be corrected as soon as the indirect toxicity effects become known, or as soon as damage becomes evident even through exposure of only slight traces.

The most important limits used for gaseous pollutants are:

Maximal emission concentration (MEC) is defined as the concentration of a substance that may be emitted from a technical establishment, given in mg m^{-3} or in $\text{cm}^3 \text{ m}^{-3}$ of air.

Maximal immission concentration (MIC) is defined as the tolerable concentration of foreign material in the air at the point of their effect, and is given in mg m^{-3} or in $\text{cm}^3 \text{ m}^{-3}$ of air, according to the state of knowledge at any given time. These values were determined for $\frac{1}{2}$ h, 1 h, and 1 yr.

Immission limit (IL) designates the average of the tolerable concentration. IL^{-1} in a year, and IL^{-2} for a brief period.

Maximal workplace concentration (MWC) was intended to take into consideration the peculiar conditions of the work site.

Technically approved concentration (TAC) These values were intended to minimize risk through contact with hazardous materials.

2.3 Pollutants in Ground and Surface Waters: Quality Parameters

In recent decades, due to the many negative experiences with water quality, efforts have been made to establish criteria for evaluating water quality and different assessment criteria for water pollution have been established. Water pollution occurs mainly because of three activities: industrial activity, which discharges refuse into the rivers and oceans, modern agricultural practices, and community wastewater.

For wastewater, two main classes of pollution can be described: residual organic matter and individual organic compounds. For municipal wastewater, organic matter can be considered to be “population equivalent,” which term refers to the amount of organic waste that a resident contributes daily to the wastewater, namely about 180 g. Numerous measurements have shown that 60 g of oxygen is removed from the water when microbial oxidation of this material occurs within 5 d at 20 °C. This amount of oxygen is designated as biological or biochemical oxygen demand (BOD₅ value). This value is usually given in mg oxygen L⁻¹ water. For example, BOD₅-values for the food/refreshment industry were larger than 5000 mg L⁻¹, while that for oil refinery was in the 97–250 mg L⁻¹ range; on the other hand, silo seepage yields values of 80,000 mg L⁻¹ and cattle urine 13,000 mg L⁻¹ [2].

Similarly, the large animal unit (LAU) is used in animal husbandry. The LAU is applied to an animal of 500 kg live weight. The organic waste of one LAU requires 800 g of oxygen when it is decomposed aerobically (13 times more oxygen than a BOD). The information acquired from the BOD₅ and LAU values are defective, while only biological materials that decompose rapidly are considered.

Another criterion is the chemical oxygen demand (COD) for the load of total oxidizable materials in wastewater. Oxidation is conducted with a potassium permanganate or with a potassium chromate acidic solution. Both methods have a weakness: a number of inorganic materials are oxidized in addition to organic compounds. Usually, BOD₅ values are approximately one half of the COD values.

The total organic carbon content is another important parameter, particularly helpful for evaluation of pollution from materials that resist microbial decomposition. The adsorbable organically combined halogens is notable, with 100 µg L⁻¹ being an usual, maximal, tolerable concentration for these compounds. Parameters for ion pollution are also valuable, usually by conductivity determination in water. Various conductivity values determine the different water types (see Table 2.1).

For the assessment of ground and surface waters, a classification according to water-goodness based on the so-called saprobic levels has been instituted (see Table 2.2). Kolkwitz and Marsson developed the “saprobic system” to determine water quality and the levels of organic waste (pollution) in rivers and streams on the basis of biological parameters, considering the abundance and distribution of 800 biological species. They defined the following concepts:

Table 2.1 Conductivity of some water types and watery solutions.^{a)}

Water types	Conductivity (mS cm ⁻¹)	Water types	Conductivity (mS cm ⁻¹)
Total desalination	10 ⁻⁴ –10 ⁻²	Surface water	0.1–10
Drinking water	0.1–1	Brakish water and sea water	1–100
Wastewater	1–10	Concentrated acids	100–1000

a) Data taken from Ref. [2].

Table 2.2 Brief characterization of the water-goodness classes.^{a)}

Criterion	Water-goodness class or saprobic level			
	Oligosaprobic	β-Mesosaprobic	α-Mesosaprobic	Polysaprobic
O ₂ -content	8 mg L ⁻¹	6 mg L ⁻¹	2 mg L ⁻¹	< 2 mg L ⁻¹
BOD ₅	1 mg L ⁻¹	2–6 mg L ⁻¹	7–13 mg L ⁻¹	15 mg L ⁻¹
Plankton	Slight	High	Moderate	Slight
Fish	Slight	High	Moderate	None
Associative types	Aerobic bacteria, algae, rotifers, planaria, spawning ground for salmon	Aerobic bacteria, algae, small crustacea, snails, numerous type of fish	Bacteria, cyano-bacteria, protozoa, leeches, a few types of fish	Anerobic bacteria, cyano-bacteria, protozoa, ciliated fungi, no fish

a) Data taken from Ref. [2].

Polysaprobic: Large amount of decaying organic matter.

Oligosaprobic: Least amount of organic waste.

α - and β -Mesosaprobic: Moderately polluted habitats.

Later, this concept was expanded to nine zones, with xenosaprobic being the least polluted and poly-saprobic having the highest level of waste. Biological water-analytical methods are based on changes in biocoenosis caused by contamination with decayable organic matter.¹

Microorganisms, with few exceptions, quickly destroy natural, organic compounds. For many synthetic organic materials, the situation is different. The microorganisms lack the enzymes necessary for their disintegration. For this reason, organic substances in water must be viewed as microbially reducible or microbially irreducible. According to this criterion they show considerable differences in their chemical behavior and their toxicity.

2.4 Pollutants in the Ground and Soil

While air and water pollution are usually clearly visible, soil pollution often goes unnoticed for long periods of time.

The concept “soil” means the complex composite of loose mineral and organic material that constitutes the layer of the earth overlying the earth’s rocky crust. Water, ice, and wind can erode the soil.

The solid phase of soil is formed by inorganic materials, organic components derived from decaying plant parts, dead animals, and microorganisms, and the humus which is composed of these microbial decomposing organic materials. Soil solids form particles of various sizes, between which are the soil pores. Some of these pores are filled with air or water and they are the basis of life for plant roots and other organisms that live underground.

The soil particles form a fine mesh that filters solid materials out of seeping water, and they serve as a storage site for materials, without releasing them into the groundwater. In addition, soil has a high capacity for regeneration. This singular property makes soil the most effective buffer against anthropogenic pollutants.

Soil hardening is a form of pollution that has consequences for its chemistry. Another change in the soil occurs by intensive ventilation in agriculture and garden farming. Moreover, certain cultivated plants have also contributed to the change in the soil.

Anthropogenic pollutant damages include: acidic damage, deposition of heavy metals and their impact on plants, deposition of pesticides and their action, pollutant deposition with sewage sludge, and deicing salts.

2.5 Sources of Emerging Pollutants or CECs

Thousands of organic compounds have been identified as CECs in the last few decades and, being new, have been largely outside the scope of regulation [3].

¹ A biocenosis describes the interacting organisms living together in a habitat (biotope).

They are implicated in multiple environmental issues: air, soil, natural waters, including oceans, rivers, lakes or groundwater, or even in drinking water. Such residues can be also found after wastewater treatment and in the sludges generated with this technology [4].

Therefore, CECs can be found in trace concentrations, ranging from a few ng L^{-1} to several $\mu\text{g L}^{-1}$ in water, sediment, soil, and biota. They show a great diversity of chemical structures, properties, and possible interaction mechanisms with living beings and they may be both natural and synthetic. The analytical techniques for detecting organic compounds in such low concentrations are continually being improved and refined, thanks especially to mass spectrometry (MS) combined with other methods and instrumentation that improves sensitivity, selectivity, and reliable determination (see Chapter 3). However, sampling and identification of CECs in various environmental matrices is often time consuming, tedious, and costly. Hence, several methods of screening for potential CECs have been proposed [3, 5–7]. The presence of CECs in the environment is attributed to several sources (see Figure 2.1).

2.5.1 CECs from WWTPs

One of the most remarkable sources of CEC is the discharge of treated wastewater from wastewater treatment plants (WWTPs). Thus, the occurrence of CECs in water is in most occasions the consequence of wastewater treatment processes. Wastewaters are produced by industries, human settlements, agriculture, hospitals, and other activities. These unregulated contaminants are present in wastewater, which are treated according to certain standards that are able to eliminate regulated contaminants and pollutants, organic matter, or pathogens. A problem arises when substances and chemicals are not able to be eliminated by the usual methods of water purification because of their own nature, or because of very low concentrations.

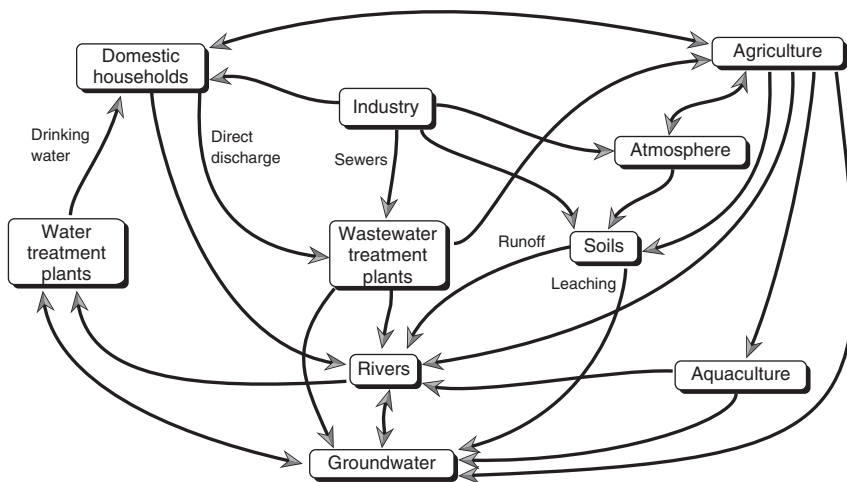


Figure 2.1 Main routes and sources of CECs.

Based on local studies there are thousands of reports about CECs on effluents and sludges produced in WWTPs. Such tests reveal significant spatial and temporal variations on concentrations, due mainly to a number of factors, such as water consumption per person and per day, environmental persistence of chemicals, and elimination efficacy of wastewater-treatment process. For common pharmaceuticals (PCs), other factors such as the rate of production, specific sales and practices, excretion rate, or the size of WWTPs, determine the amounts of such compounds [8, 9].

To date, the occurrence of CECs has been much better detected and characterized in wastewater and surface water bodies compared to groundwater [10, 11].

However, the main classes of micropollutants in the aquatic environment may be found and belong to the usual groups of CECs analyzed in other zones of the environment.

Pharmaceuticals: NSAIDs, lipid regulators, anticonvulsants, antibiotics, β -blockers, and stimulants.

Personal care products: Fragrances, disinfectants, ultraviolet (UV) filters, and insect repellents.

Steroid hormones: Estrogens.

Surfactants: Non-ionic surfactants.

Industrial chemicals: Plasticizers, fire retardants.

Pesticides: Insecticides, herbicides, and fungicides.

2.5.2 CECs in Wastewater Biosolids

On the other hand, contaminants removed from wastewater are frequently transferred to sludge and finally to biosolids. The so-called biosolids consist of sludge obtained in WWTPs that has been transformed into a solid residue by removing water and properly treated to eliminate pathogens. The result is a stabilized organic waste, rich in carbon, nitrogen, oxygen, and other nutrients. Biosolids are often applied to agricultural soils such as conditioners or fertilizers, and these materials are a source of CECs if they are not being treated. For example, a local study performed at the Roger Road Wastewater Reclamation Facility in Tucson (AZ, United States (U.S.)) looked at the fate of one class of compounds, that is, PBDEs. After wastewater treatment followed by disinfection with chlorination, it was found that 85–95% of the PBDEs, which are used as flame retardants, were transferred from the wastewater to the biosolids during wastewater treatment [12].

2.5.3 CECs from Agriculture and Livestock

Agrochemicals are used in bulk in modern agriculture. The use and handling of most pesticides and other agrochemicals are regulated. The constant development of markets and the introduction of new substances render agriculture and livestock a vast source of new contaminants. CECs may be incorporated into the agricultural environment *via* a number of routes (see Figure 2.2). (i) “Concentrated animal-feeding operation” which are able to produce residual concentrations of antibiotics, hormones, and other veterinary compounds that are released

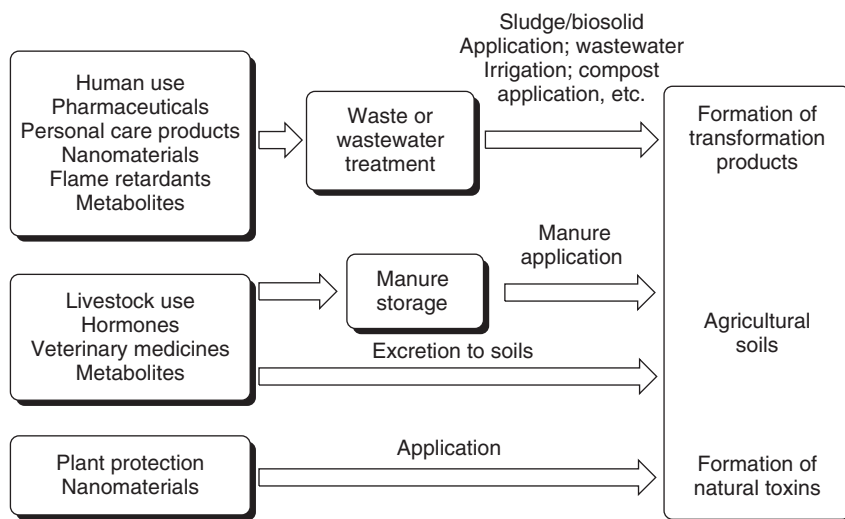


Figure 2.2 Main migration processes to soil.

directly to the environment. (ii) Indirect input during the application of manure, biosolids, or other solids waste material to soil. On the other hand, livestock of concentrated animal feeding operation produces slurries containing CECs that can be leached to soil. Once in the soil, CECs may be transported to water bodies by leaching, runoff, and drainage. The extent of the transport depends on the persistence of the CEC and on how it interacts with the soil and sediment particles. In some cases, treated wastewater, containing CECs from human activity, can be incorporated into the soil.

2.5.4 CECs in Soils

Soil is considered a non-renewable natural resource, but over centuries humans and their activities have increased soil contamination, especially since the Industrial Revolution. Soil contaminants harm soil microbiota that are directly related to the conservation of biodiversity and other remarkable functions such as recycling of nutrients. However, microbial communities may be surprisingly resilient and/or functionally redundant. Likewise, the potential toxicity of soil contamination to humans is controversial, and investigations on the mix of different contaminants are very limited. International guidelines, such as the Stockholm convention on POPs, have established a list of priority contaminants, but the influence or effects of CECs remain unknown.

Most chemicals in soils may be linked to soil particles by non-bonding forces, and may stay attached to the surface or even move inside such particles. The phenomenon is known as sorption and is the key factor for the retention of chemicals in soil or, by contrast, move to running waters or groundwaters and determines the fate and degradation of most organic compounds in soils. For traditional pollutants, such as pesticides or POPs, the research and monitoring of the mechanisms and time course of such compounds in relation to sorption in soils is well

known. These compounds interact with the organic carbon matter in the soil and sorption behavior can be mostly predicted based on the hydrophobicity measurements and the attractive forces of the pollutant to organic materials of the chemical, and the result can be predicted and quantified by certain equations.

Most of these equations appear to be valid for many CECs, but there are many other CECs, such as human and veterinary products or certain nanomaterials, that behave differently. In these cases the sorption process can vary markedly, according to different soil types and these differences in sorption of a given compound in different soils cannot be explained by interactions with organic carbon, but with the fact that many PCs can exist in natural environments in both the ionic and non-ionic forms [13]. Therefore, they can interact with other soil constituents as clay particles or metal oxides, and the sorption properties of the soil, such as pH becomes the determinant.

Many CECs in soils come primarily from manure and slurry and these matrices of CECs may also alter their behavior and their transport through soils. They can influence the sorption behavior of veterinary and human drugs or other CECs such as personal care products (PCPs) and may also affect sorption persistence [14, 15]. In some, these effects can be attributed to the main factor mentioned earlier, that is, changes in pH or alterations in the nature of dissolved organic carbon in the soil/manure system.

The degradation of chemicals including CECs is an aerobic process. However, other degradation physicochemical transformations such as photolysis, hydrolysis, or oxidations take place [16].

2.5.5 CECs in Groundwater

Many residents worldwide use groundwater as a source of drinking water. For example, in the United States, approximately 40% of the population drink water pumped from aquifers. Groundwater is vulnerable to contamination from infiltration from septic systems and WWTPs effluents. This type of contamination is remarkable in case of unconfined sand and gravel aquifers. Some reports have revealed that many organic compounds can be detected in groundwater sources [17], but in comparison to surface water, groundwater was found to be less contaminated with micropollutants [18, 19]. A large variety of CECs have been detected in groundwaters globally at environmentally significant concentrations ($\approx 100 \text{ ng L}^{-1}$) but the occurrence of CECs in groundwater is poorly characterized around the world except in some parts of Europe and North America.

Some studies have been biased toward potentially contaminated sites, so that the actual frequency and distribution in groundwater remains largely unknown [11]. Contamination of groundwater takes place mainly from several mechanisms such as landfill leachate, groundwater–surface water interactions, infiltration of contaminated water from agricultural land, or seepage of septic tanks and sewer systems. In the case of landfill leachates or septic tank leakages, concentrations of CECs are generally in a range from 10 to 10^4 ng L^{-1} and 10 to 10^3 ng L^{-1} , respectively [11].

Subsurface flow and transport are capable of attenuating a large proportion of CECs, by processes such as dilution, adsorption to aquifer material, degradation, and travel time [20], but once they invade groundwaters, CECs may stay for decades because the special conditions of groundwater such as low microbial populations and low redox activity increase residence times of such compounds as compared to that in surface waters. Detected compounds were also the most common ones found in surface water and wastewater [21].

In Europe, the EU Water Framework Directive 2000/60/EC [22] and its daughter Groundwater Directive 2006/118/EC [23] established environmental objectives for protecting groundwater as well as the water bodies and ecosystems dependent on groundwater. The USEPA published a new contaminant candidate list (CCL-4), in 2016, which included four pharmaceuticals (erythromycin, *N*-methyl-2-pyrrolidone, quinoline, and nitroglycerin) as well as perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), and 10 hormones: 17 α -estradiol, E2, EE2, 19-norethisterone, equilenin, equilin, estriol (E3), estrone (E1), mestranol, and norethindrone.²

2.5.6 CECs in Landfill

Landfills are another source of CECs. These facilities are the final repository of waste from several origins, for example, from residential, industrial or commercial activities. Waste in landfills is composed of very heterogeneous materials that may have negative effects on the environment, including surface water, groundwater, soil, and air, and ultimately on human health. The EU directive 1999/31/EC [24] defining the different categories of waste applies to all landfills designated as waste-disposal sites for the deposit of waste onto or into land. The following wastes may not be accepted in a landfill, according to this regulation: liquid waste, flammable waste, explosive or oxidizing waste, hospital and other clinical wastes that are infectious, used tyres, with certain exceptions, or any other types of wastes that do not meet the acceptance criteria laid down in an Annex to the Directive.

Landfills may produce leachates containing a complex mixture of contaminants, including CECs that are often discharged to pathways that ultimately may lead to groundwater, streams, and receiving waters such as WWTPs. The typical composition of landfill leachate [25] has a BOD₅ ranging from 20 to 57,000 mg L⁻¹ and a COD of 140 to 152,000 mg L⁻¹, together with heavy metals including, Cr, Cd, Co, Hg, Pb, Ni, and Zn and nonmetals such as As, found in landfill leachates at varying concentrations.

A study on fresh leachate from 19 landfills in the conterminous United States, detected a total of 129 out of 202 CECs, including 62 prescription pharmaceuticals, 23 industrial chemicals, 18 nonprescription pharmaceuticals, 16 household chemicals, 6 steroid hormones, and 4 plant/animal sterols [26–28]. To prevent and reduce environmental impact of this source of CECs, two strategies can be followed:

1. Treatment of landfill leachate to reduce the load of CECs.
2. Reduction in the mass of discarded items containing CECs.

² <https://www.epa.gov/ccl/chemical-contaminants-ccl-4>.

The presence of CECs in landfill leachate makes it necessary to improve treatment methods, increasing advanced treatment, because concentrations of CECs identified in landfill leachates are substantially higher than that in municipal wastewater [29].

2.5.7 CECs in Seawater

Oceans and seas in the past years have become potential sources of energy, for raw materials, or in food production, among other things. There is a clear relationship between increasing human settlements (and therefore human population density) and environmental changes in coastal regions. Coastal waters are considered the final destination for waste produced by industry, agriculture, and urban effluents. CECs are transported to coastal areas *via* riverine inputs and effluents from WWTPs, except for some residues used in mariculture [30–32]. Intensive agriculture and livestock or aquaculture produce large amounts of waste, which contain CECs, presenting a real ecological risk to aquatic organisms, because marine ecosystems receive many chemical pollutants through direct discharges, those transported by rivers, or from atmospheric deposition.

Therefore, these ecosystems are exposed to ecological hazards. Regulated contaminants are relatively easy to detect and control. For instance, two deals, the Convention for the Protection of the Marine Environment of the North-East Atlantic and the European Marine Strategy Framework directives [33] are international agreements in this regard. The problem arises with CECs [34]. In marine waters, CECs represent a real threat to the aquatic environment. Possible effects such as acute and chronic toxicity to aquatic organisms, accumulation in the ecosystem, and loss of habitats and biodiversity and as well as threats to human health could arise [35].

Pollution of marine media becomes particularly relevant in the case of foods from the sea, because seafood is consumed worldwide in huge quantities and low-quality seawaters can be a formidable source of harmful environmental chemicals such as polychlorinated biphenyls, dioxins, pesticides, metals, and of course CECs [36]. The presence of these substances in seafood is attracting increasing attention from the scientific community and regulatory authorities, because the presence of any detectable contaminant in seafood for human consumption at levels above the regulations is an undeniable risk that may have a negative impact on the health of consumers, especially over the long term. The maximum levels for a range of contaminants are regulated, for example, PAHs, polychlorinated biphenyls (PCBs), certain toxic elements, and certain marine toxins. Legislation and monitoring programs are dealing with the supervision of such substances and, therefore, seafood is periodically tested for the presence of a selection of environmental contaminants. So far, the focus has been mainly on well-known conventional pollutants. Nevertheless, there is growing awareness concerning the presence and potential effects CECs in seafood [37].

The information currently available on the concentration of several CECs in seafood is rather fragmented, as happens with most of the reports on CECs. The results are not consistent, which may hinder seafood risk assessment.

Nevertheless, a single European database,³ based on information collected from scientific literature, reports, and monitoring programs of CECs in seafood, has been developed within the CEC safe SEAFOOD project [34].

2.6 Treatment of CECs

2.6.1 Treatment of CECs in WWTPs

One of the main sources of CECs are the effluents of WWTPs, which are not regulated and the concentrations in such effluents are very low. Therefore, most urban WWTPs do not have appropriate methods for CECs removal [21].

Conventional wastewater treatment applied to urban wastewater remains ineffective for most CECs, because they remain in effluents along the sequential processes of WWTPs. Relatively high removal rates (20–50%) are found only in case of compounds with $K_{ow} > 4$ at pH = 7–8 as some PC molecules [38]. However, other techniques have great potential for removing CECs from WWTPs effluents.

2.6.1.1 Physical Methods

Adsorption on activated carbon is a general and effective procedure for eliminating most organic compounds of low and medium molecular weight from a fluid and both powdered and granular activated carbons may be widely used in adsorption processes. Powdered activated carbon is considered an effective adsorbent for eliminating most persistent/non-biodegradable organic compounds. An advantage of using powdered activated carbon is its affordable procedure because it can provide fresh adsorbent media continuously or can be used seasonally or occasionally when there is a high risk of trace organics.

Membrane filtration is a separation process based on the use of semipermeable membranes that work as specific filters letting water flow through, while retaining suspended solids or dissolved substances, depending on pore diameter when pressure is applied. Selectivity is defined according to parameters such as retention or separation factor, and productivity is expressed by a parameter called flux, which is the flow rate of the filtrate.⁴ Selectivity and productivity are membrane-dependent. Membrane processes are classified as microfiltration, ultrafiltration, nanofiltration, or reverse osmosis, depending on their removal mechanism and target contaminants (see Figure 2.3).

These removal mechanisms depend largely on a number of factors, such as membrane process type, membrane characteristics, operating conditions, the characteristics of specific molecules, and membrane fouling [39]. The retention of CECs in membrane processes can generally be achieved by size exclusion, adsorption onto membrane, and charge repulsion. Microfiltration and ultrafiltration are proven processes to efficiently eliminate turbidity, but CECs are generally poorly removed during microfiltration and ultrafiltration, because the membrane pore sizes of CECs are much larger than their molecular sizes.

³ <http://www.ecsafeseafoodbase.eu>.

⁴ Expressed by the unit: $\text{L m}^{-2} \text{h}^{-1}$ or $\text{L m}^{-2} \text{d}^{-1}$.

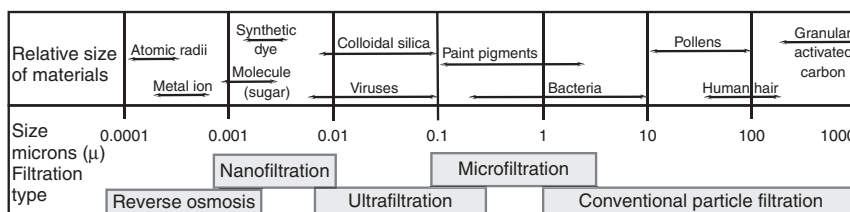


Figure 2.3 Scheme with different types of filtrations, displaying the sizes of well-known items.

However, they can be removed via adsorption onto membrane polymers, as well as interaction with natural organic matter in wastewater [40]. This process can take place at low temperatures, with relatively low energy cost because most of the energy that is required is used to pump water through the membrane.

Membrane bioreactors are devices that combine both biological treatment and membrane filtration of activated sludge, generally microfiltration and/or ultrafiltration. Membrane bioreactors possess the following advantages over conventional wastewater treatment [41]. This procedure effectively removes a wide spectrum of organic compounds in very low concentrations including compounds that are resistant to conventional activated-sludge processes [42]. This is because:

- Sludges retain many compounds by adhesion.
- The membrane can also intercept the compounds.
- A longer sludge retention time in membrane bioreactors may improve microbial degradation of many organic molecules in water [43].

The removal of CECs in membrane bioreactors can be affected by the composition of the wastewater concentration of contaminants, pH, conductivity operating temperature, sludge age, or existence of anoxic and anaerobic compartments [44].

2.6.1.2 Chemical Methods

Advanced oxidation processes such as ozonation and H_2O_2 /Fenton oxidation are useful methods for CECs removal. Both are efficient technologies that demonstrate some superiority over conventional treatments having disinfecting effects, which are essential for possible reuse of treated water [45]. O_3 can degrade organic contaminants directly and indirectly by formation of radical $\text{HO}\cdot$, a nonselective oxidizing agent capable of destroying many molecules. Radical $\text{HO}\cdot$ can also be formed in water with H_2O_2 , Fenton's reagent,⁵ and UV light. Some CECs are oxidized by both ozone and radical $\text{HO}\cdot$ (e.g., naproxen and carbamazepine), whereas some are only subject to radical $\text{HO}\cdot$ (e.g., atrazine and meprobamate) and some are resistant to both forms of oxidation (e.g., tris(2-chloroethyl) phosphate (TCEP) and tris(chloropropyl) phosphate (TCPP)) [46].

⁵ Fenton's reagent is a solution of hydrogen peroxide with ferrous iron as a catalyst that is used to oxidize contaminants or waste waters.

2.6.1.3 Biological Methods

Attached-growth technology is a promising alternative to conventional activated-sludge processes for wastewater treatment. In an attached-growth treatment, a biofilm attaches to and covers the support packing material. Such a biofilm is formed by microorganisms, particulate material, and extracellular polymers [47]. The attached-growth systems can be classified into two major groups:

- Fixed bed bioreactors.
- Moving bed bioreactors.

The attached-growth processes offer the following six advantages over conventional activated-sludge processes in wastewater treatment [48]:

- They improve oxygen transfer for the treatment with a higher nitrification rate and higher biomass concentrations.
- They are more effective in organic removal and can apply high organic-loading rates in a relatively shorter hydraulic retention time.
- They allow the development of microorganisms with relatively low specific-growth rates.
- They are less subject to variable or intermittent loadings.
- Smaller reactor size and less space are required.
- Operational costs are lower.

Biofiltration is a general procedure for removing organic contaminants, when the effluent is passed through a filter or column (biofilter) containing an inert support with microorganisms adsorbed onto the surface, which are able to transform organic compounds. Specific strains of bacteria may be used to degrade specific compounds. This technique provides notable advantages over conventional activated carbon adsorbers. Biofilters are self-regenerating by continuous microorganism growth, and therefore maintain their adsorption capacity over a long period of time, and contaminants are actually removed, and not retained, by biological transformations. Biofiltration appears to be a promising biological technique for CECs removal [49].

In recent years, European authorities have been studying to upgrade WWTP protocols with additional tertiary or complementary treatment steps such as oxidation by ozonation and/or treatment of effluents with activated-carbon adsorption to remove CECs from treated water as a measure to improve water quality [22].

2.6.2 Treatment of CECs in Landfill Leachates

Landfill leachates are one of the most remarkable sources of contaminants including CECs that may affect soil, runoff, and consequently surface waters and groundwaters. The treatment of such waste should constitute a real improvement in environmental quality. The characteristics of a typical landfill leachate are as follows: a BOD_5 from 20 to 57,000 $mg\ L^{-1}$ and a COD of 140 to 152,000 $mg\ L^{-1}$, and variable concentrations of heavy metals and other elements such as As. Applicable techniques for CECs are similar to those for wastewater, membrane

bioreactors [50], and ozonation due to the high redox potential of ozone. Microbial treatment of dissolved organic matter and active PC ingredients stemming from landfill leachates is in most cases not effective in simple lagoons and conventional biological reactors [51]. It is necessary by molecular biology techniques to enumerate microbes capable of degrading CECs.

2.6.3 Wastewater Reuse

Fresh water is a limited natural resource. Wastewater reuse is a key factor for sustainable water management. Thus, treated wastewater is widely reused and is actually considered as a reliable alternative water source for the recharge of aquifers, recreative use, or irrigation, pathways entering into the water cycle. The so-called urban-water cycle presents some differences with respect to the natural water cycle, because it includes reuse of water and recharge of aquifers with the corresponding presence of CECs along the cycle (see Figure 2.4). The urban water cycle may be described in four steps:

1. Effluents, after wastewater treatment may be fed into the water supply system (indirect reuse).

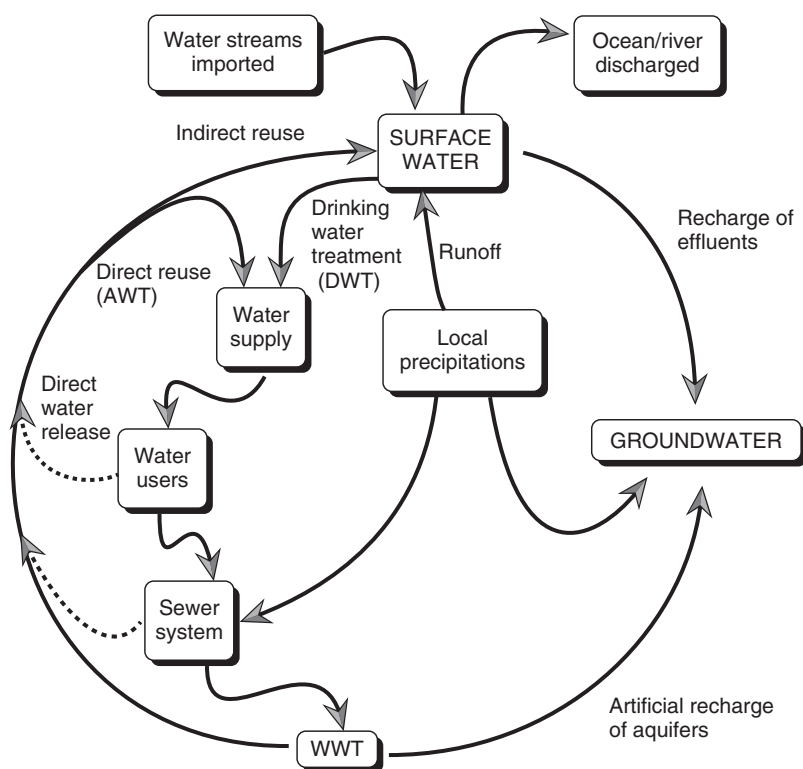


Figure 2.4 Scheme of a generic urban water cycle. Dotted lines indicate untreated water release

2. Wastewater effluent treated by advanced processes to meet drinking-water standards (e.g., by reverse osmosis).
3. Effluent is discharged into surface water from where it infiltrates into aquifers (bank-filtration) that serve as both storage and distribution systems for potable water.
4. Effluent is treated to high standards such that it can be used for aquifer recharge (soil-aquifer treatment).

The possible impact of CECs on reused water depends on the use of water, irrigation, recreation, or drinking. In many areas fresh water is a very limited resource.

As described in Section 2.6.1, the conventional treatments for wastewater purification fail to completely remove most pollutants found in water in low or very low concentrations (micropollutants) such as antibiotic-resistant bacteria and/or their genes, and others. For this reason, the actual effects of reusing treated water containing CECs remain unknown on ecosystems, especially in a long-term scenario. Although reuse offers a number of benefits related to the enhancement of water balance and soil nutrition, a number of questions remain open regarding this practice.

A key problem is the presence CEC detected in drinking water worldwide. The source of most of these compounds is generally attributed to contamination from municipal wastewater. The number of publications with regard to the occurrence of micropollutants in drinking water remains limited [19]. Traditional water-sampling methods often require large amounts of water in order to detect contaminants in trace concentrations, and recent studies have shown that most micropollutants in waters obtained in the final stages of drinking water treatment were below the limit of quantitation or limit of detection [52–54], because drinking-water treatment plays a significant role in eliminating most contaminants from water [55, 56], with some CECs remaining in trace concentration. In most studies [19, 52–54], the maximum concentrations of most micropollutants have been reported to be below 100 ng L^{-1} , with only some exceptions. For example, Kleywegt *et al.* [53] detected carbamazepine at a concentration exceeding 600 ng L^{-1} , more than 10-fold higher than those of most other compounds.

2.7 Toxicity of CECs

Toxicity is the degree to which a substance can damage an organism. It depends on the nature of the compound, the dose, and the exposition time. Humans, animals, plants, and the ecosystem as a whole are exposed to many chemicals, both natural products and synthetic compounds. Some can be considered contaminants and other as pollutants. Regulated pollutants are usually subject to strict controls and regulations internationally and doses dangerous to humans or ecosystems are generally well known, as also their effects on the environment and in many cases how to mitigate these effects. (see Figure 2.5)

Although limits are necessary, they need to be applied critically under the assumption that they ensure safety. Some observations will show that despite

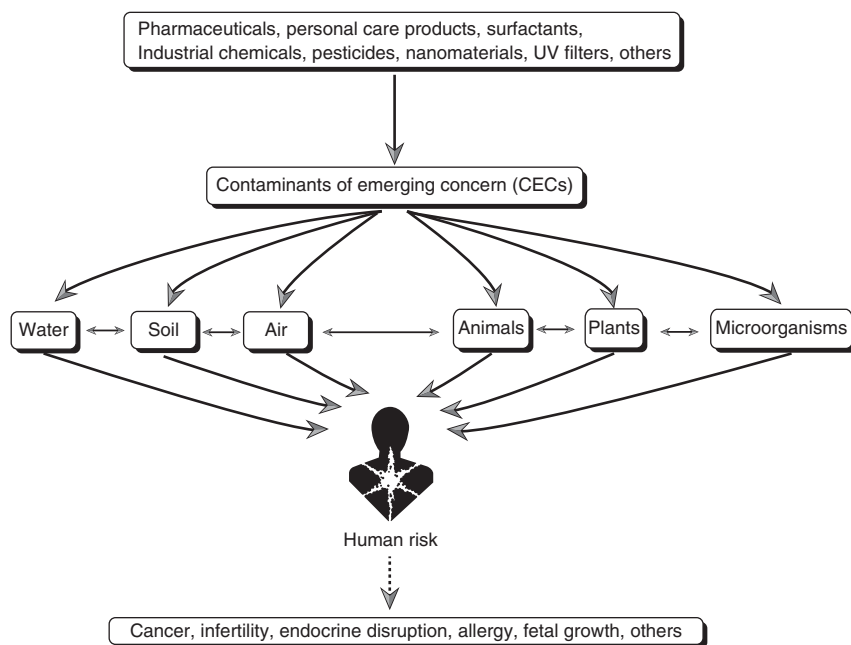


Figure 2.5 Scheme of the impact of CECs on the environment and in humans.

the amount of such substances, no recognizable symptoms of disease appear, although certain alterations in metabolism processes may occur over the long term. Pollutant detection always refers to individual substances, but in reality the population is usually exposed to a combination of hundreds of substances, and the effect of such combinations may differ from the sum of the effects of the individual substances (termed “cocktail effect”).

CECs are continuously released or discharged in the soil, in water, or into the air, by several mechanisms so that they are detected in ecosystems, although in very low concentrations. Based on research, CECs may present suspected mutagenicity, teratogenicity, and carcinogenicity to humans and other animals when concentrations are high. However, many studies conducted on associations between emerging contaminants and adverse effects on the human body have shown that there is no sufficient or large-scale evidence to prove causal associations between CECs and mutagenicity, teratogenicity, and carcinogenicity in humans [57].

In case of chemicals that cause endocrine disruption, studies examining possible effects in humans have yielded inconsistent and inconclusive results, which is responsible for the overall data being classified as weak [58]. Many studies on wildlife have been conducted in areas where it is known that the levels of environmental chemicals are high. Many of the challenges encountered in assessing the risks of endocrine disrupting chemicals (EDCs) to human health are also relevant to wildlife species. However, there are unique challenges in determining the potential effects of EDCs on wildlife as compared with humans, including

Table 2.3 Organic wastewater compounds detected in 20 public supply wells on Cape Cod, Massachusetts.^{a)b)}

Compound	% of wells	Maximum concentration (ng L ⁻¹)	Health-based guideline values (ng L ⁻¹)	Maximum in other United States public source waters (raw water) (ng L ⁻¹) ^{c)}
Prescription drugs (non-antibiotics)				
Antipyrine	5	1	n.a.	< 1
Atenolol	5	0.8	70,000	36
Carbamazepine	25	72	12,000, 40,000	<11, 2, 9, 51, 156, 190
Gemfibrozil	5	1.2	14,000	<13, <15, 4, 17, 24
Meprobamate	20	5.4	260,000	73
Phenytoin	20	66	2000 ^{b)}	29
Prescription drugs (antibiotics)				
Sulfamethizole	5	1	n.a.	<50
Sulfamethoxazole	60	113	18,000,000	2, 12, 41, 58, 110
Trimethoprim	5	0.7	6,700,000	<13, 1, 4, 11, 20
Other organic wastewater compounds				
DEET	5	6	200,000	<500, 16, 110, 410
Organophosphate flame retardants				
TBEP	5	50	n.a.	300, 400, 960
TCEP	15	20	3300	<500, <500, 260, 530
T CPP	20	40	150,000	720
TDCPP	5	10	n.a.	<500, 170, 260
TEP	25	20	n.a.	n.a.
Perfluorosurfactants				
PFOA	10	22	40, 300, 400	31
PFOS	40	97	200, 300	16, 41
Alkylphenols				
4-Nonylphenol	14	20 ^{d)}	n.a.	<5000, 130, 4100

a) Data taken from Ref. [17].

b) Not available, n.a.

c) Source waters suspected to be contaminated by other than WWTPs or domestic wastewater were not included.

d) Estimated value, below method reporting limit.

the large number of potential target species, varied life history strategies, differences in physiological mechanisms, and lack of basic understanding of endocrine regulation for many species. Similar conclusions can be drawn for other families of CECs.

The current understanding of the effects of CECs on wildlife and humans remains incomplete, especially for a long-term perspective because the control and later elimination of emerging contaminants in the environment and human body depends on future techniques and studies to establish overall remediation theories and methods. According to research findings in recent years on the presence of CECs in soil, wastewater effluent, surface water, groundwater, and even sometimes in potable water, an effort to detect and follow possible effects on ecosystems and human health over the long term must be considered, and regulatory framework should take this into account. For example, the concentrations of CECs in water supplies studied in the city of Cape Cod, Massachusetts, show values much lower than those established by the guidelines (see Table 2.3) [17].

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3

Detection and Analysis of Chemical Pollutants

3.1 Introduction

EPs can be found (ng L^{-1} levels) in several media, both natural and anthropogenic, for example, in wastewater, soil, air, or tissues of living organisms. A complete knowledge of the problems presented by EPs is attributed to the advances in analytical methods that have enabled the detection of molecules in quantities so low that for many years such products went unnoticed because detection techniques were unable to measure concentrations in the ranges of ppb or ppt either in environmental samples or in biological samples. These low levels, which have been detected with efficient modern analytical methods, are in all cases below toxicity levels that affect human health. One of the first instances of detecting unexpected pollutants in locations far from the emission point took place in marine animals sampled from Swedish waters in 1966 [1], when PCBs and DDTs were found.

One fundamental technique for conducting environmental analysis has been gas chromatography (GC), which enables organic compounds considered pollutants to be detected in several matrices. However, conventional GC techniques have been restricted mainly to uncharged nonpolar compounds of a certain volatility, and during the first years of environmental analysis, polar compounds had to be analyzed by gas chromatography/mass spectrometry (GC/MS) after being chemically transformed into more volatile derivatives.

Fortunately, in the past decade, liquid chromatography/mass spectrometry (LC/MS) has evolved to offer more easy and more efficient procedures that have revolutionized environmental analysis by providing new analytical tools capable of identifying both polar and unpolar organic compounds, in the ng L^{-1} range without the need for derivatization, in all kinds of matrixes including water bodies (wastewater, surface water, groundwater, and drinking water) or in solid samples (sewage sludge, manure, soil, or sediments).

3.2 Sample Preparation

Sample preparation for EP analysis is fundamental for a proper study of these harmful substances [2]. In many cases, samples are collected from the respective matrix to gather useful and reliable data pertaining to that specific matrix.

The very low concentrations of analytes, the diversity of sample collection conditions, and the necessary concentration procedures hamper the isolation of the analyte. An added task emerges in many cases because the concentrations of pollutants do not remain constant throughout the evaluation periods. Therefore, values may fluctuate during the collection period and often reference materials are not available for accurate detection and evaluation. In such situations, sample preparation must be processed as quickly as possible and by the simplest methods available. To maximize the amounts of analytes extracted and minimize possible interferences, the determination of pollutants requires prior extraction and cleanup steps in order to apply the appropriate analysis technique. Thus, sample preparation is often the most laborious and longest step in the process of detecting EPs.

According to green chemistry tendencies, ionic liquids have been used as an alternative to conventional organic solvents for both extraction and chromatography applications to improve selectivity and efficiency in extraction and separation techniques [3].

3.2.1 Extraction with Organic Solvents

Liquid-liquid extraction (LLE) and continuous LLE can be applied for the isolation of a variety of hydrophilic organic molecules considered as pollutants. A wide range of organic solvents such as petroleum ether, pentane, hexane, cyclohexane, dichloromethane, or toluene can be used to partition an organic compound from a matrix such as soil or water. After the extraction, it is necessary to reduce the extracted volume and it is very common to derivatize the isolated samples for prior analysis. Continuous LLE offers a great advantage over conventional LLE, because it uses smaller amounts of solvent and shorter extraction times.

3.2.2 Microwave-Assisted Extraction (MAE)

Microwave-assisted extraction (MAE) can be used to extract many classes of pollutants, including EPs [4]. Compared to other procedures this technique dramatically shortens the extraction time, and can be used with small volumes of samples. Depending on the microwave equipment, multiple samples can be extracted simultaneously with open or closed vessels.

The application of MAE for extraction of EPs from the environmental matrices has been an attractive method used over the past few years [5]. MAE uses microwave energy to irradiate the liquid sample in contact with the solvent. The application that the microwave uses is non-ionizing radiation, which causes molecules to move by migration of ions and rotation of dipoles. The effect of the microwave energy is dependent on the nature of the matrix and the solvent used [6]. However, the principle of MAE is based on the impact of microwaves on molecules caused by dipole rotation and ionic conduction. MAE has the advantage of decreasing the extraction time and the sample volume for the extraction of organic analytes from solid samples [7]. Another advantage is that, when available, MAE is suitable for the analyses of solid samples such as soil, sewage sludge, food, and sediments.

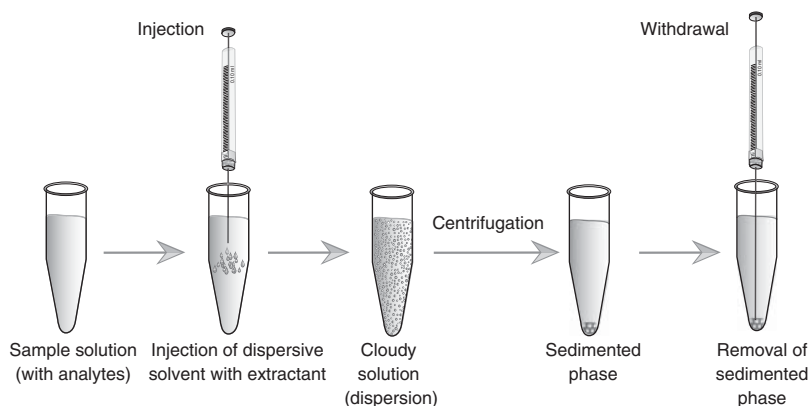


Figure 3.1 Schematic representation of the DLLME method [8].

3.2.3 Dispersive Liquid–Liquid Microextraction (DLLME)

In dispersive liquid-liquid microextraction (DLLME), analytes are extracted by the dispersion of the extracting solvent made in water [8]; for dispersion, a second solvent (the dispersing solvent) is used. The extraction process involves two steps, as follows (see Figure 3.1):

- A mixture of extracting and dispersing solvents is rapidly injected into a water sample. A dispersion is formed, which facilitates fast extraction of analytes from the water sample.
- The dispersion is removed by centrifugation and the extracting solvent containing analytes is taken for analysis with a microsyringe.

3.2.4 Vortex-Assisted Liquid–Liquid Microextraction (VALLME)

The technique termed VALLME is a very fast sample-preparation method with the inherent advantage of achieving equilibrium conditions within only a few minutes. During this time, a mild emulsification is carried out by the mixing of a low-density organic phase with an aqueous phase using a vortex dispersion of the extraction solvent, which enhances the mixing than does ultrasound irradiation. The highest number of applications of the VALLME procedure has been carried out in aqueous samples, and the method has been used to detect chemicals, specifically micropollutants in many matrices, as shown in Figure 3.2 [9].

3.2.5 Single-Drop Microextraction

Single-drop microextraction (SDME) has become a widely preferred liquid-phase microextraction technique because it is inexpensive, easy to operate, and nearly solvent-free. Essentially, SDME combines extraction (and, conceivably, cleanup) and concentration in a minimum number of steps and, followed by direct extract introduction into an analytical system with a micro-syringe equipped with a needle bearing a drop of a water-immiscible organic solvent. There are two versions of this technique:

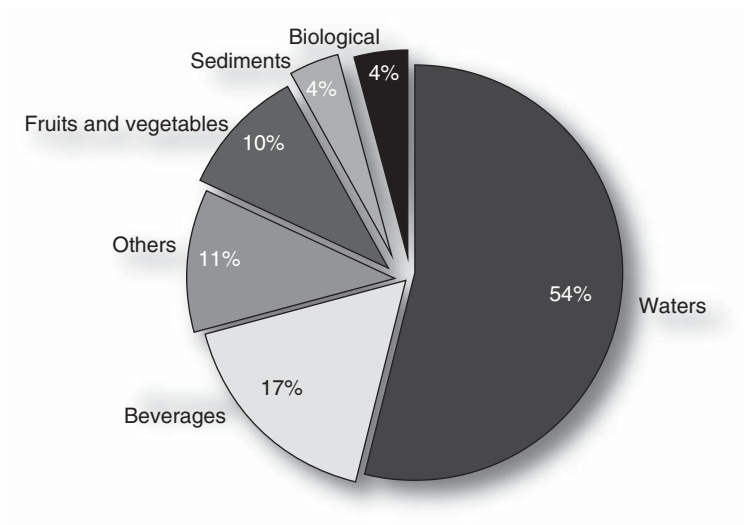


Figure 3.2 Application of VALLME percentage (%) in different sample sources. (Data taken from Ref. [9].)

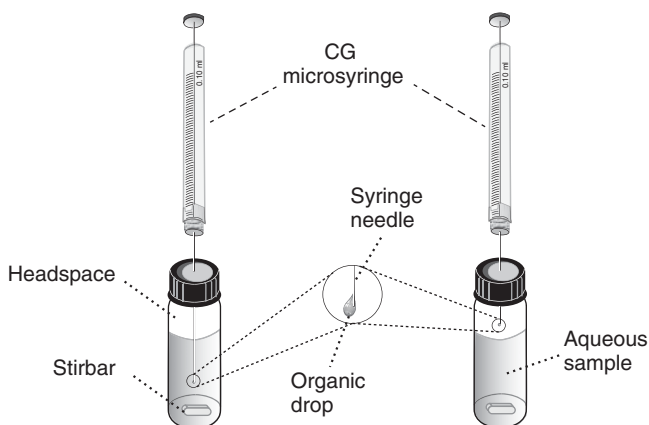


Figure 3.3 Single-drop microextraction (SDME) procedures. (a) Direct immersion (DI) and (b) headspace (HS).

- Direct immersion (DI)–SDME (static mode). In this case, a 1.3 μL microdrop of a water-immiscible organic solvent is immersed into a large flowing aqueous drop to perform the extraction process [10] (see Figure 3.3).
- Headspace (HS)–SDME. This technique considers the organic droplet in the aqueous sample solution, which is most suitable for the consideration of volatile or semi-volatile analytes (see Figure 3.3).

3.2.6 Solid-Phase Extraction (SPE)

Solid-phase extraction (SPE) is a technique for analyte isolation, which uses solid particles such as chromatographic packing material, usually contained in a

cartridge type device. It chemically separates the different components of a sample. SPE provides rapid and selective sample preparation and purification, prior to a more exhaustive and specific chromatographic analysis. Using the same principles of liquid chromatography (LC) to control selectivity in analyte isolation, SPE provides sample clean-up, recovery, and concentration necessary for accurate quantitative analysis of the target product. The multitude of available phase chemistries can be packed into an array of hardware formats.

SPE is one of the most widespread methods for sample preparation. For many pollutants that cannot be partitioned into an organic solvent, showing poor extraction efficiency, SPE is used in preference to extraction methods. Sampling with the SPE method requires very low amounts of solvents and simpler procedures than is required with classical extraction methods and, in addition, automation of the process is possible. Commercial devices for SPE extraction are available in three basic formats: thin flat discs, small cylindrical cartridges, and well plates. Each format of the SPE device can be used with a wide variety of sorbents: silica gel bases, hydrophilic–lipophilic balanced, mixed cation, anionic exchange, or polymeric graphitized carbon black.

Modified C_{18} silica gel is used as a universal extraction sorbent. It works within a 2–8 pH range, and the retention mechanism is due to the hydrophobic interactions between the analytes and the C_{18} alkyl chains. Once the cartridge is prepared, a volume of sample from 0.1 to 2 L is passed through the SPE cartridge in a 10 mL min^{-1} flow, by gravity, syringe-push or vacuum-induced. Afterwards, the cartridge is dried and extracted using solvents either pure or as mixtures, depending mainly on analyte polarities.

3.2.7 Solid-Phase Microextraction (SPME)

Solid-phase microextraction (SPME) is a very simple and efficient, solventless sample-preparation method, invented by Pawliszyn [11]. The SPME device is designed to be silica-fiber coated with a thin layer (5–100 nm) of a suitable polymeric sorbent or immobilized liquid. The coated fiber is placed inside a needle, itself placed within a syringe-like arrangement. SPME can be used for the direct extraction of analytes from a gaseous or a liquid medium by immersing the fiber from the syringe into the sample. It can also be used indirectly for analyzing the composition of liquid and solid samples by extracting the analytes from the HS above them (HS-SPME) (see Table 3.1). This technique allows the analysis of a broad spectrum of analytes, with particular emphasis on the sampling of polar analytes from polar matrices [12].

3.2.8 Dispersive Solid Phase Microextraction (DSPE/DSPME)

This is a modification of SPME, a highly developed form of SPE, when sorbents such as bonded silica, activated carbon, and primary secondary amines are dispersed directly into the sample solution instead of being packed in SPE columns. It consists in a sequential extraction with a SPME followed by a clean-up process when adsorbent-containing analytes are separated by filtration or centrifugation [13]. The technique looks greener than in similar methods and is applicable in a wide range of environmental samples such as food, water, and soil.

Table 3.1 SPME fibre coatings classification and preparation procedures [12].

Coatings (commercially available)	New coatings Sample source	Fibre coating (preparation procedure)
PDMS PA PDMS/DVB CAR/PDMS CW/DVB CW/TR DVB/CAR/PDMS	Polypyrrole coatings Other coatings Mesoporous silica Molecularly imprinted polymers Ionic imprinted polymers Immunsorbents Sol–gel coatings	Electrochemical procedures Molecular imprinting Sol–gel technology Physical deposition On-fiber derivatization M-SPME

Molecularly imprinted SPE is an extraction technique based on the use of synthetic cross-linked polymers with artificially generated recognition sites, which predetermine its selectivity for a given analyte. These are able to specifically rebind a target molecule in preference to other closely related compounds produced by the polymerization of monomers around a template molecule, leading to a highly cross-linked three dimensional network polymer [14]. The monomers are chosen based on their ability to interact with the functional groups of the template molecule, which is extracted from the source. By this technique, binding sites, with shape, size, and functionalities complementary to the target analyte, are established onto the polymer to give a very robust material, which is stable in a wide range of conditions of pH or temperature. The greatest difficulty arises from choosing the monomer in order to ensure the appropriate selectivity of the target compound.

3.2.9 Matrix Solid-Phase Dispersion (MSPD)

In the matrix solid-phase dispersion (MSPD) [15] method, a previous LLE is carried out using an absorbent material with a clean-up performed in the elution step with florisil, followed by MS identification and quantification of the substances using both GC/MS in selected ion monitoring (SIM) mode and tandem liquid chromatography mass spectrometry/mass spectrometry (LC-MS/MS) in positive ionization mode (see Figure 3.4). This methodology has been employed in the case of pesticide detection in vegetable oils, which present serious difficulties in sample preparation.

3.2.10 Passive Sampling

Passive sampling can be defined as any sampling technique for environmental monitoring of waterborne and airborne pollutants (organic or inorganic) in the free flow of analyte molecules. This technique is carried out from the sampled medium to a receiving phase in a sampling device, as a result of a difference between the chemical potentials of the analyte in the two media. The net flow of analyte molecules from one medium to the other continues until equilibrium is established in the system, or until the sampling period is stopped

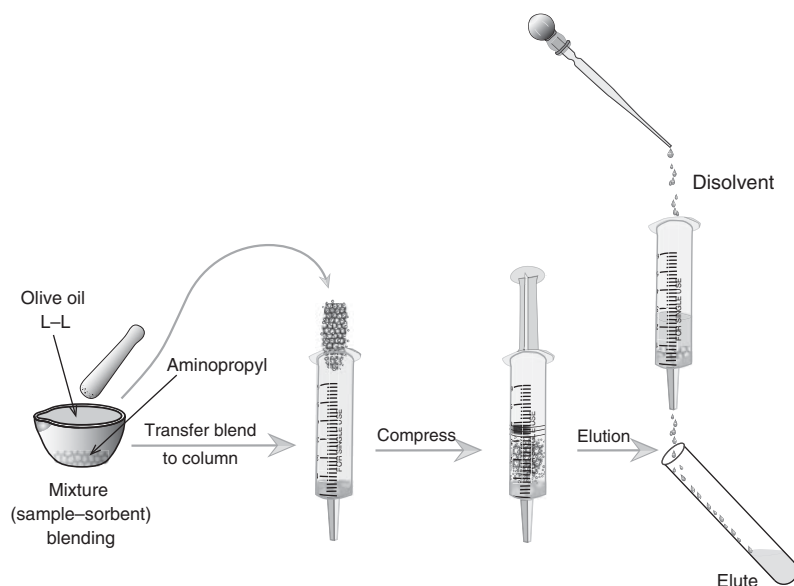


Figure 3.4 Schematic representation of the MSPD method [15].

[16]. Many specific devices to perform this technique have been adapted in each case. Passive sampling devices have been used since the 1970s to measure time-weighted average or equilibrium concentrations of pollutants in various environmental matrices (e.g., air, soil, sediment, and water). The popularity of using such samplers has increased and the technology is now well established for measuring atmospheric pollutants [17].

3.2.11 Immunosorbent Extraction

Immunosorbents have been used to analyze micropollutants in water. For example, it is a useful selective method for detecting and quantitatively determining pesticides, PCs, or PAHs as a step prior to high-performance liquid chromatography (HPLC) or GC. The antibody of the immunosorbent is immobilized on an inert support of silica gel and used as an affinity ligand in the sample extraction from water.

3.2.12 Extraction of Volatile Compounds

Sample preparation to detect volatile or semi-volatile organic compounds can be performed by several techniques such as SPME either by DI or by HS. HS is a sample-preparation technique for GC that is used for the analysis of volatile and semi-VOCs in solid, liquid, and gas samples. Volatile sample components diffuse into the gas phase forming a HS gas in the GC vial. In both cases, the procedure includes active sampling by cartridges with sorbent-packed tubes or methods based on passive sampling. Once the analytes are collected, they can be recovered for further analysis by solvent extraction or thermal desorption. Other techniques available for sample preparation of such compounds are LLE

and purge-and-trap method in which an inert gas is bubbled through a portion of the aqueous sample at ambient temperature, and the volatile components are efficiently transferred from the aqueous phase to the vapor phase for further GC analysis.

3.2.13 Online Extraction

Some online methods for collecting samples of pollutants have been developed. Although automated online SPE has been used for relatively clean matrices such as surface waters, online SPE in more complex systems such as effluents of WWTPs still remains a challenge.

SPME has been used in the preparation of online samples with certain efficiency and with multiple parallel extractions by means of an automatic robotic unit. In this case, the amount of analyte is proportional to the volume of the extraction phase. For example, 96 parallel extractions are capable to detect amounts of analyte of low ng mL^{-1} . This online procedure requires relatively expensive equipment, and therefore pretreatment of samples are often required.

3.2.14 Extraction with Nanomaterials

Nanomaterials (NMs) show great potential for the monitoring and remediation of pollutants. The use of NMs in the extraction as well as microextraction of pollutants from a matrix has grown rapidly in recent years [18]. Such methods are proving to be promising not only for sample preparation for removing of pollutants with carbon nanotubes (CNTs), zeolites, nanofibers, and nanocomposites, but also because they may help to simplify the analytical methods, due to their high surface-to-volume ratio, reactivity, and mechanical, thermal, or electronics properties. For example, magnetic nanoparticles (NPs) are easily removed from any media [19].

3.2.15 Sampling from Biological Materials

Samples from biological materials are usually not directly compatible with chromatographic techniques because they usually have high complexity and protein content, and thus are frequently absorbed in the stationary phase. This results in a substantial loss of column efficiency and greater back pressure. A scheme that reflects the total analytical method for complex biological and environmental samples should be similar to that shown in Figure 3.5.

3.3 Analytical Methods for Identifying EPs

Protocols detecting EPs in comparable conditions, that are accepted by international organizations or countries have become a key subject all over the world. These protocols are valuable tools for possible forthcoming regulations, and attempt to establish a consensus related to such pollutants, from the EPA, EU, and WHO.

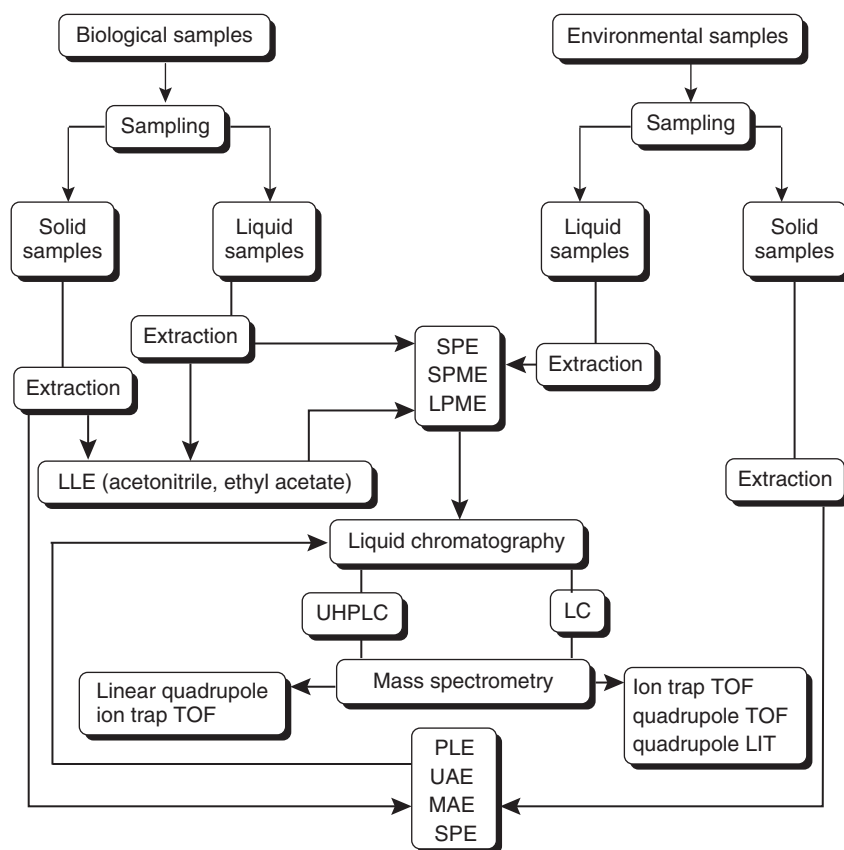


Figure 3.5 Analytical methods for biological and environmental samples [20]. (Sosa-Ferrera, <https://www.hindawi.com/journals/bmri/2013/674838/abs/>. Licensed under CC BY 3.0.)

MS is the most valuable detection technique, because it provides information on the molecular structure of the compounds and it is highly sensitive and selective. The combination of chromatography and MS can separate complex mixtures or organic compounds into their individual components and subsequently analyze each compound in the mixture both qualitatively and quantitatively.

A considerable number of analytical methods, such as GC/MS, LC-ESI-MS/MS or HPLC–MS/MS, have appeared in the literature in the last few years for analyzing organic compounds, specifically organic pollutants [3, 21, 22].

HPLC is the dominant modern analytical technique employed to analyze single organic compounds and their mixtures. Technical improvements have been made during the past years in terms of sensitivity to detect traces of compounds in all kinds of organic analytes in both environmental and biological samples [20]. At the same time, demand for high-throughput analysis is growing due to an increasing number of samples, and shortening of the analytical run times is often required. Three main modern approaches in HPLC methods enable the reduction of analytical time without compromising resolution and separation efficiency: the

use of monolith columns, LC conducted at high temperatures, and LC at ultra-high pressures using columns packed with sub-2-micron particles [23, 24].

For quantification, the SIM mode of MS can be used to achieve high sensitivity. The extraordinary interest in applying LC/MS techniques has led to a significant improvement in mass-analyzer technology. However, when highly complex matrices are investigated, triple quadrupole MS is required to improve the determination selectivity and the unequivocal identification of the target molecules [25]. The required instruments used in tandem MS are able to isolate every molecular ion of the compound of interest in the first stage of the mass analyzer. The most intensive fragment ion from the precursor ion is used for quantification. A less-sensitive secondary transition is used as the second criterion for confirmation purposes. Triple quadrupole features a wide linear range of at least three orders of magnitude.

3.3.1 Separation Methods

SPE remains the most widely used means of extraction and concentration, and new SPE sorbents are available, including ion-exchange resins and hyper-cross-linked polymer resins, which are being used to capture a broader range of analytes within a single extraction. Solventless extraction techniques, such as SPME, also continue to be used in many applications [3].

One new extraction trend is the application of ionic liquids for extraction. They are being used in hollow fiber-liquid phase microextraction and in single-drop microextraction [3].

Separation of non-VOCs ideally requires a method that avoids derivatization, does not chemically alter the organics during separation, and has high resolving power and high sensitivity of detecting separated compounds. While no single method meets all of these criteria, HPLC approaches this ideal to an extent and is the method of choice for the separation of non-VOCs [26].

A variety of fractionation procedures have been used prior to HPLC [27]. However, Ultra-HPLC (UHPLC) continues to be the most commonly used. UHPLC uses small-diameter particles (typically 1.7 μm) in the stationary phase and short columns, allowing higher pressures, narrower LC peaks (5–10 s wide), improved chromatographic separations, and dramatically shorter analysis times (often to 10 min or less). Two-dimensional GC ($\text{GC} \times \text{GC}$) is also increasingly used [3].

3.3.2 Characterization Methods

Most of the classical characterization methods, for example, nuclear magnetic resonance (NMR), infrared (IR), and UV spectrometry, are unsuitable for characterization, and necessarily some type of MS must be employed. Conventional electron impact MS considerably extends the types of compounds that can be handled by GC/MS. However, electron impact suffers from two limitations: the compound of interest has to be volatilized prior to ionization, and the molecular ion is frequently of low intensity with respect to fragment ions. The first limitation can be overcome to some extent by rapid heating. The second limitation, however, is difficult to solve and results in extremely complex, overlapping mass spectra in the case of mixtures [26].

One of the latest trends continues to be the use of high-resolution mass spectrometry (HRMS) with LC to identify unknown contaminants. In this regard, application of orbitrap and time-of-flight mass spectrometers is increasing. NMR spectroscopy is being used more as a complementary analytical technique to confirm tentative structures proposed by LC/HRMS and LC-MS/MS [3].

Recently, more advanced MS technologies, such as time-of-flight (TOF)-MS or linear ion trap (LIT)-MS, have been introduced. New hybrid quadrupole/TOF-MS allows the acquisition of full-scan production spectra. Based on the production spectra, the structural elucidation of unknown compounds as well as the identification of target compounds can be achieved with a much greater degree of certainty [28].

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4

Overview of Pharmaceutical Products as Emerging Pollutants

4.1 Introduction

For many years, studies on the impact of chemical pollution have focused almost exclusively on conventional “priority” pollutants, especially pesticides and industrial intermediates that display persistence in the environment. Another diverse group of bioactive chemicals that have received comparatively little attention as potential environmental pollutants includes PCs. Literature shows that many of these compounds eventually survive biodegradation, when discharged into bodies of water. Many of these compounds and their metabolites are ubiquitous and persist in the environment.

In 1999, Daughton and Ternes [1] published a special report entitled “Pharmaceuticals and Personal Care Products in the Environment: Agents of *Subtle Change*?” raising a warning on the repercussions of PC products in the environment.

According to the USEPA, PCs refer to prescription and over-the-counter therapeutic drugs and veterinary medicines which contain PCs whose pharmacological effects provide significant benefits to society. PC drugs are chemicals used for diagnosis, treatment (cure/mitigation), alteration, and prevention of disease and to address problems related to health conditions or the structure/function of the human and/or animal body. They belong to the compounds called “micro-pollutants” because they are often found in the mg L^{-1} or ng L^{-1} values in an aquatic environment.

The ubiquitous use of PCs in human and veterinary medical practices, aquaculture, and agricultural products has led to the continual release of a wide array of PC chemicals into our environment. Batt *et al.* [2] conducted a national-scale survey of the occurrence of PCs in surface waters in the United States. The survey included 182 sampling sites and targeted rivers. Of the 46 analytes, reported,¹ 37 were detected in at least 1 sampling location. The antibiotic (sulfamethoxazole) was the most frequently detected compound, its concentrations ranging up to

1 These analytes include antibiotics, diuretics, antihypertensives, anticonvulsants, and antidepressants.

570 ng L⁻¹. Ten of the compounds were detected in 20% or more of the sampling sites.

PCs do not consist of a uniform group of substances with similar chemical, physical, structural, biological, and toxicological properties. PCs are mainly identifiable by their use: a substance is identified as a PC only if it is used as a medicine for humans or animals. In this sense, chemical substances may be divided into two classes, those that are used as PCs and those for which a possible pharmaceutical use has not yet been discovered. For example, nitroglycerin, initially sold as an explosive, has subsequently been used as a PC. Thus, it is clear that any chemical substance, either natural or synthetic, might be used as a PC and that all substances are capable of causing harm to the environment or to human health at some concentration. Approximately 3000 different substances are used as PC ingredients, such as painkillers, antibiotics, antidiabetics, β -blockers, contraceptives, lipid regulators, antidepressants, and impotency drugs. However, only a small subset of these compounds have been investigated in environmental studies so far.

PCs are a class of micro-pollutants that have aroused a special interest at the end of the twentieth century due to major improvements in analytical science. PCs can now be detected at ng L⁻¹ concentrations in the majority of surface waters whereas previously they were present but could not be detected. The major difference between PCs and other substances found in the environment is that they have been designed to be biologically active. PCs attracted special attention for two main reasons:

- 1) Sumpter *et al.* [3] in their investigation of fish feminization in UK rivers had identified that EE2, a PC used in birth control and hormone replacement therapies, was probably a contributory factor to this effect and, in laboratory studies, had been shown to be active even at few ng L⁻¹, similar to concentrations then being detected in surface waters.
- 2) It was recognized that data on the ecotoxicology of PCs was very sparse with little information on chronic effects. The question that then arose was: are all PCs as ecotoxicologically potent as EE2 or is EE an exception? If EE2 was not exceptional, then, on the levels of pharmaceutical residues in the aquatic environment, there might be a serious problem. Since 2000, a multitude of articles and reviews have arrived at broadly similar conclusions.

According to Barceló and Petrovic [4], researchers need to pay attention to PCs for the following reasons:

- Because of their continuous introduction into the environment, via effluents from sewage treatment plants STPs and from septic systems, PCs are referred to as “pseudo-persistent” contaminants.²
- PCs are developed with the intention of performing a biological effect.

² High transformation/removal rates are offset by their continuous introduction into the environment.

- PCs often have the same type of physicochemical behavior as other harmful xenobiotics.³
- PCs are used by humans in rather large quantities, similarly to the use of pesticides.

Powerful chromatographic-detection techniques enabling detection up to the ng L^{-1} level allowed researchers to quantify a large number of PCs in the environment, thus compelling the scientific community to consider this contamination type as a potential issue of concern [5].

4.2 Therapeutic Classes of PCs Detected in the Environment

Normally, PCs are classified according to their therapeutic purpose and biological activity⁴ (see Chapter 5 for further information).

4.3 Sources of PCs in the Environment

Among the emerging contaminants, PCs are one of the most predominant groups of substances in the environment due to their universal use and their physicochemical properties. According to the biological effects of PCs, they can be potentially dangerous to living beings. Scientists demonstrated the presence of PCs in the environment more than 30 years ago. Several reports have shown that the amount of PCs in the environment has strongly increased [6–8].

The PC industry uses the term of PCs to describe products that are pharmacologically active, resistant to degradation, highly persistent in aqueous medium, and potentially adverse for water organisms, with a negative impact on human health [9].

Few data are available on the total worldwide use of PCs. The consumption and application of PCs may vary considerably from country to country [10]. WHO has published a report on 2011 on world consumption of major types of PCs.⁵ The global pharmaceutical sales during the 2013–2015 period, by region (in billion U.S. dollars) are shown in Figure 4.1.

Several hundred thousand t yr^{-1} of PCs are estimated to be used for the treatment of human and animal diseases [11, 12], as well as in livestock and aquaculture [13, 14]. Worldwide, the use of prescription and nonprescription drugs are estimated in one thousand t yr^{-1} [15, 16].

PCs are conceived primarily for particular physiological modes of action and commonly to resist inactivation before exerting their intended therapeutic effect. However, these same properties are paradoxically responsible either for bioaccumulation and toxic effects in aquatic and terrestrial ecosystems [17, 18].

³ Persistence in order to avoid the substance from becoming inactive before having a curing effect, and lipophilicity in order to be able to pass through membranes.

⁴ For example, antibiotics, analgesics, antineoplastics, anti-inflammatory substances, antibiotics, antihistaminic agents, X-ray contrast media, etc.

⁵ http://www.who.int/medicines/areas/policy/world_medicines_situation/en/.

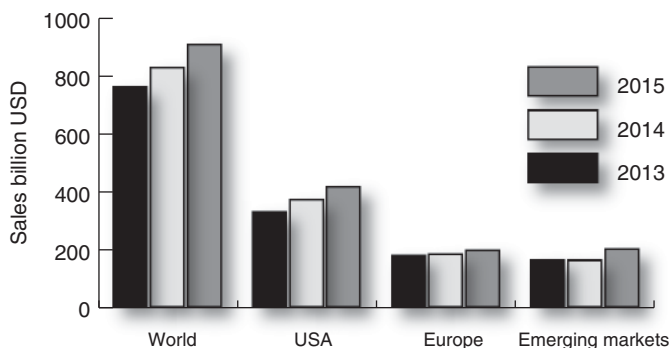


Figure 4.1 Global PCs sales during the 2013–2015 period by region.⁶

As opposed to the conventional, persistent priority pollutants, PCs need not be persistent if they are continually introduced to surface waters, even at low ppm/ppb concentrations (ng-pg L^{-1}), which might give rise to toxicity even without high persistence rates [19, 20].

The source of the PCs can be divided into two types: point source pollution and diffuse pollution.

Point source pollution: This is a single identifiable source which originates from separate locations and can be calculated in mathematical modeling [21]. For instance, industrial effluents, hospital effluents, and STPs as well as septic tanks are the major point sources for soil zone and water resource pollution.

Diffuse pollution: This source is hard to identify and occurs over broad geographical areas [21]. One example is the runoff, including agricultural runoff from animal waste and manure, urban runoff from domestic waste, and the leakage from waste treatment systems and plants [22]. Compared to point source pollution, diffuse pollution has generally lower environmental loading because it has higher potential for natural attenuation in the soil and subsurface [23].

As illustrated in Figure 4.2, PCs have several routes through which to enter the environment, such as human or animal excreta, wastewater effluents, treated sewage sludges, industrial wastes, medical wastes from health-care and veterinary facilities, landfill leachates, and biosolids [24].

The main sources from which PCs are released into the environment are from the medical and therapeutic treatment of humans and livestock. PCs are usually absorbed and completely or partially metabolized whereas residues of the active ingredients and their metabolites are excreted in the urine and feces as “parent compounds,” “conjugated compounds,” or “metabolites.” The excrement is flushed either directly into domestic septic systems or into municipal WWTPs. They can also reach the environment through inappropriate disposal of unused and expired products [25], through effluent discharge from STPs, and runoff from agricultural soils receiving biosolid amendments/animal farms and livestock, aquaculture industry, and so on [26]. Treated effluents, and in some

⁶ Data taken from <https://www.statista.com/statistics/272181/world-pharmaceutical-sales-by-region>.

⁷ Such as pesticides, detergents, fuels, etc.

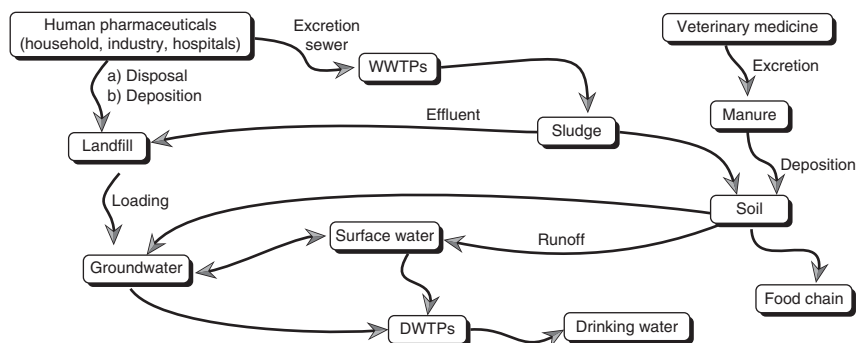


Figure 4.2 Principal contamination routes of PCs.

cases untreated wastewater, may take many routes into the environment, but the ultimate destination is the aquatic environment, including small streams, rivers, lakes, and the marine waters [27, 28].

PCs can be excreted without being transformed or metabolized by biochemical reactions by two pathways [29]:

- A first pathway involves oxidation, reduction, hydrolysis, and alkylation reactions.
- In the second pathway, glucuronide or sulfate conjugates are formed and excreted through the urine in the form of more polar and hydrophilic derivatives (as a metabolite or as a mixture of metabolites).

Flushed PCs and their metabolites end up in the sewage system and pass through an STP. In WWTPs, the removal efficiency depends heavily on the chemical characteristics of the PCs [30]. The acid/base properties of a molecule are among the most fundamental for drug action. For example, Figure 4.3 depicts the chemical structure of some acidic drugs detected in the environment [31].

After administration, PCs can be excreted both unmetabolized or as active metabolites leading to concentrations of up to $\mu\text{g L}^{-1}$ in surface waters of developed countries [32] and of up to mg L^{-1} in developing countries [33].

Holm *et al.* [34] and Ahel *et al.* [35] identified landfills, where household waste and pharmaceutical waste were disposed of, as sources for contaminating groundwater with PCs. Furthermore, pharmaceutical production sites have been identified as sources for PC contamination [36, 37].

According to the EPA, other sources of PCs in the environment include leakage from underground sewage systems, overflow of untreated sewage from storms and sewer systems failure following malfunction, land application of biosolids for soil amendment and fertilization, and discharge of untreated sewage from homes into surface waters.

4.4 Detection and Analysis of PCs in the Environment

Detection of PC pollutants in the aquatic environment has resulted partially from an increase in social interest in environmental problems, arising mainly from their biotic and abiotic recalcitrance after discharge into the environment [6, 38].

The growing worldwide interest in reported detections of very low concentrations of PCs in various environmental matrices, including the

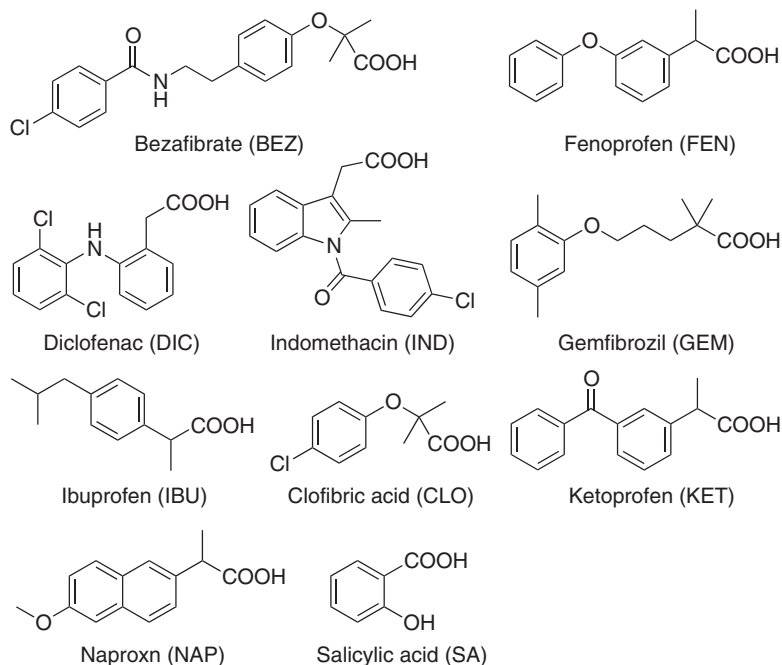


Figure 4.3 Chemical structure of some acidic drugs.

water cycle,⁸ is attributable mainly to the remarkable recent development and improvement of analytical equipments and methods [39, 40].

Methods for analyzing PCs in water samples are diverse. A comprehensive overview of current approaches to trace pharmaceutical residues in sludge, wastewater, and surface water is given by Buchberger [41]. Since the first detection of PCBs and DDTs in marine animals from Swedish waters in 1966 [42], GC has been the basic tool for environmental analyses of various organic pollutants, although sometimes it has been carried out with derivatization. However, GC techniques are restricted primarily to uncharged nonpolar compounds with some volatility. GC/MS or tandem gas chromatography-mass spectrometry/mass spectrometry (GC-MS/MS) and LC/MS or LC-MS/MS are advanced methods capable of determining target compounds up to the ng L^{-1} level and are commonly applied to detect PCs in water or wastewater. However, analytical methods to determine pharmaceutical residues in fish or other biota samples are quite scarce [43]. The selection of methods depends on the physicochemical properties of the target compound. LC-MS/MS analysis is more suitable for measuring target compounds that are more polar and highly soluble in water, whereas GC-MS/MS is appropriate for more volatile target compounds.

Because their concentrations in the aquatic environment are quite low (the ng L^{-1} to $\mu\text{g L}^{-1}$ range), a highly sensitive and highly selective multicomponent

⁸ For example, surface water, groundwater, treated wastewater effluent, and drinking water.

method for simultaneous analysis is indispensable for detecting and quantifying these products. The development of new analytical techniques has enabled to determine PCs at concentration of even few ng dm^{-3} [44].

To analyze PC pollutants coexisting in river- and sewage-water samples together with many other substances, in the ng L^{-1} to $\mu\text{g L}^{-1}$ range, samples need to be concentrated to the $\mu\text{g L}^{-1}$ level, which is the concentration detection limit of LC/MS and LC-MS/MS [45, 46].

In particular, the widespread use of SPE-LC-MS/MS, which is a versatile and reliable method for detecting and quantifying PC pollutants, has helped to reveal the presence of pollutants in trace concentrations (ng L^{-1} to $\mu\text{g L}^{-1}$ range) that had been difficult to detect by conventional analytical methods [39, 40].

Novel methods applied by Klosterhaus [9], using LC/MS and GC/MS, were validated for low-level detection of 104 PCs in environmental samples.⁹ For PCs, the USEPA Method 1694 [47] was modified to include additional compounds and extended to the analysis of tissue matrices. Maximum concentrations were 92 ng L^{-1} in water (valsartan), 33 ng g^{-1} dw in sediments (triclocarban), and 14 ng g^{-1} ww in mussels (*N,N*-diethyl-*m*-toluamide). This study represents the first reconnaissance of PCs in mussels living in an urban estuary and provides the first field-derived bioaccumulation factors for select compounds in aquatic organisms.

In 2010, Huerta-Fontela *et al.* [48] established an analytical method based on SPE for wastewaters. Pintado-Herrera *et al.* [49] developed a multianalyte method based on microextraction for the simultaneous determination of a wide range of PCs in aqueous and solid matrixes. A limit of detection down to 1 ng L^{-1} and 0.1 ng g^{-1} could be achieved. A multiresidue method has been developed by Baker and Kasprzyk-Hordern [50] for determining 65 PCs and illicit drugs in aqueous matrixes from raw and treated wastewater to river water. Detection limits down to 0.5 ng L^{-1} were reached for compounds. Ferrer and Thurman [51] developed an analytical method for the analysis of 100 PCs and their transformation products in surface water.

4.5 Occurrence of PCs in the Environment

In the EU, ≈ 3000 different substances are being used in medicine [52]. During and after treatment, humans and animals excrete a combination of intact and metabolized PCs. Consequently, many bioactive compounds enter into water bodies without any tests for specific environmental effects [53].

Although PCs have been present in water for decades, their levels in the environment have only recently begun to be quantified and acknowledged as being potentially hazardous to ecosystems [11, 54].

The occurrence of PCs in the environment has been widely discussed and published [55–75]. Several studies report the occurrence and detection of extremely low concentrations of PCs in very complex matrices in liquid and solid states [76, 77], in influents [78–80] and effluents [30, 81, 82] from STPs, in wastewater

⁹ Surface water, sediment, and mussel tissue samples collected from San Francisco Bay, CA, USA.

[6, 83–85], in surface water (rivers, lakes, streams, estuaries, among others) [6, 82, 86–97], groundwaters [66, 98–101], seawater [102], in drinking water [103–107], in the aqueous environment [44, 103, 108, 109], and in the marine environment [28]. Their occurrence in soil [110], sediments [93, 96, 111–114], milk [115], meat [116], in wild-caught fish [117], and in caged mussels [118] has also been confirmed.

4.5.1 Pharmaceuticals in WWTPs

Municipal wastewater is one of the main exposure routes that brings PCs used by humans into the environment, because people in private households are either excreting PCs during the normal course of treatment or are improperly disposing off unused or expired drugs in toilets. After their release into the sewage system, these products pass through WWTPs. PCs that do not readily biodegrade enter the receiving waters as dissolved pollutants via the effluents of WWTPs [119, 120].

Wastewater PCs are especially challenging due to their relative solubility and high mobility in aqueous environments compared with many other wastewater contaminants; designed high bioactivities and long shelf-lives (biorecalcitrance); and wide range of potential ecological endpoints including, toxicity [121, 122], endocrine disruption [123, 124], immunomodulation [125, 126], antibiotic resistance selection [127, 128], as well as cytotoxicity and mutagenesis [129, 130].

Therefore, the efficiency with which WWTPs can remove PCs used by humans is crucial. The concentration of PCs in sewage effluents depends not only on the effectiveness of the treatment but also on location and seasonality, as it is shown in Table 4.1.

Considerable research has reported that WWTPs that meet the regulatory requirement for wastewater treatment are only moderately effective in removing the PCs, except for the plants with a tertiary treatment [132, 133]. PCs have been detected in the ng L^{-1} to $\mu\text{g L}^{-1}$ range [134, 135]. Therefore, more than 25 PCs are still found in effluent wastewater and sludge samples.

4.5.2 PCs in Hospital Wastewater

To a minor but relevant extent, hospitals are one of the main sources of these pollutant emissions sent to WWTPs. Hospital wastewater is almost always untreated before being discharged into urban wastewater networks and then into municipal WWTPs [136], despite the fact that these plants are not designed to remove these types of compounds efficiently [137]. Although some PCs entering WWTPs are removed (e.g., biodegradation or adsorption onto sludge), a sizeable amount is released into the environment [138].

Hospital wastewater is about 2–150 times more concentrated in some micro-pollutants depending on the therapeutic class of the PC [139]. The separate treatment of hospital wastewater allows the specific degradation of these pollutants since they could be more accessible for biological treatments [140]. PCs are found at high concentrations (up to mg L^{-1}) in hospital wastewaters [141, 142]. Discrepancy in the literature are found considering hospital wastewaters as the most important source of these types of pollutants in the

Table 4.1 Detected PCs concentration (ng L⁻¹) in the waters of the Ter river (N Spain) in three sampling campaigns.^{a),b)}

Compound	WWTP effluent (January)	WWTP effluent (May)	WWTP effluent (August)
Paracetamol	<MQL	n.d.	111
Ibuprofen	n.d.	n.d.	83
Naproxen	347	97	297
Salicylic acid	n.d.	114	82
Meloxicam	240	735	n.d.
Ketoprofen	399	39	n.d.
Tenoxicam	696	19	n.d.
Piroxicam	391	87	197
Diclofenac	347	184	397
Codeine	53	<MQL	112
Indomethacine	92	n.d.	90
Phenazone	n.d.	9	21
Ciprofloxacin	370	104	55
Azithromycin	287	31	111
Ofloxacin	165	157	33
Clarithromycin	238	19	41
Sulfamethoxazole	n.d.	n.d.	19
Trimethoprim	n.d.	10	11
Erithromycin	<MQL	14	37
Venlafaxine	5587	364	2027
Paroxetine	150	386	n.d.
Citalopram	66	49	34
Trazodone	n.d.	<MQL	112
Carbamazepine	n.d.	16	130
Atenolol	529	53	239
Metoprolol	235	129	143
Nadolol	39	14	n.d.
Gemfibrozil	297	178	76
Bezafibrate	3	7	n.d.
Atorvastatin	n.d.	27	n.d.
Valsartan	149	58	90
Irbesartan	526	10	149
Losartan	380	42	65
Furosemide	395	252	217
Hydrochlorothiazide	1688	287	1132

(Continued)

Table 4.1 (Continued)

Compound	WWTP effluent (January)	WWTP effluent (May)	WWTP effluent (August)
Levamisole	68	34	32
Thiabendazole	n.d.	12	n.d.
Ranitidine	259	118	150
Iopromide	<MQL	573	n.d.
Xylazine	n.d.	92	n.d.

a) Data taken from Ref. [131].

b) The non-detected (n.d.) compounds were considered as zero, and halves of method quantification limit (MQL) values were applied for the compounds at concentration <MQL.

WWTP influents [141]. Nevertheless, contrary results indicate that the amount of PCs by the hospital effluent is insignificant compared to the large flow and the low concentration of PCs present in urban wastewater were also reported [143].

Orias and Perrodin [144] have identified 15 compounds in hospital wastewater, at high concentrations (mg L^{-1}). Some of these PCs present a considerable threat for aquatic organisms even at very low concentrations.

4.5.3 PCs in Surface Water and Groundwater

The primary sources for PCs entering surface water are from excretion and bathing through treated or untreated municipal wastewater effluent discharged into receiving surface water bodies together with improper disposal of pharmaceutical waste and excess medication by consumers as well as health-care and veterinary facilities into sewers and drains [88, 145].

PCs used in veterinary medicine are excreted onto the ground or directly into surface waters without passing through a WWTP, making their control and follow-up much more challenging. PCs used in fish farms are directly released into surface water [17].

PC contamination of groundwater is a substantial concern in effluent-dominated streams, due to high aqueous mobility, designed bioactivity, and effluent-driven hydraulic gradients. Strong hydrologic connectivity was observed between surface water and groundwater [146].

Several assessments have documented substantial downstream transport of wastewater contaminants including PCs, illustrating the threat to downstream drinking-water supplies in effluent-impacted streams [147–150]. Considerable attenuation of PC contaminants was reported in effluent-impacted streams in the U.S. United States [151–153], but half-lives on the order of hours to days nevertheless represented substantial downstream transport.

The occurrence of some PCs in surface water, STPs/WWTPs and groundwater from America, Europe, and Asia, has been summarized and shown in Table 4.2, using data from several studies. The PCs shown in Table 4.2 are those with high frequency detection in the effluent, surface water and groundwater. From

Table 4.2 Concentration (ng L⁻¹) of some PCs in different water types and regions.

Compound	America		Europe		Asia	
	Effluent, WWTP/STP ^{a)}	Freshwater– rivers, canals ^{b)}	Groundwater ^{c)}	Effluent, WWTP/STP ^{d)}	Freshwater– rivers, canals ^{e)}	Groundwater ^{f)}
Trimethoprim	2550	145	18	39	59	2000
Ciprofloxacin		77	0.28	499	n.d. ⁱ⁾	2050
Sulfamethoxazole	310	170	458	185	33	38
Naproxen	1550	555			80.5	397
Ibuprofen	11,900	203	3.97	8000	468	1600
Paracetamol			1890		40	30
Ketoprofen		16		940	293	128
Diclofenac	4200			740	794	1760
Salicylic acid				3170	184	24
Carbamazepine	1550	735	420	150	366	3600
Caffeine			290	300	568	4500
References	[154, 155]	[156, 157]	[158, 159]	[160, 161]	[162, 163]	[164, 165]
						[166, 167]

a) New Mexico, Balkan.
b) New Jersey, Canada.
c) California, Canada.
d) Spain, Italy.
e) Spain.
f) Pan-European.
g) Taiwan, Korea.
h) Taiwan, Vietnam.
i) Non-detected (n.d.).

Table 4.2, it can be deduced that generally, the concentrations of PCs decrease from the effluent of STPs to the groundwater and freshwater resources. This is probably because natural processes, for example, biotransformation, photolysis, sorption, volatilization, and dispersion, can attenuate PCs in the surface water [168]. Therefore, the concentrations of PCs at the effluent of STPs are generally higher.

Other studies have reported the presence of more than 80 drugs, including active and inactive metabolites in the surface waters of various countries of the EU, the United States, Brazil, and Canada [169, 170]. In studies conducted on the groundwater below the city of Barcelona (Spain), the highest frequency of detection and abundance of pharmaceutical transformation products TP were observed in an aquifer zone that receives water from a river severely impacted by WWTP discharges [171, 172]. Overall, TP concentrations in the aquifer were lower than in the river, due to dilution and transformation of these compounds in the subsurface. However, occasionally, groundwater concentrations exceeded river concentrations. This suggests that either some parts of the aquifer may act as reservoirs or that specific compounds are slowly transported or retarded within these aquifer zones [172, 173].

In Italy, several studies investigating the occurrence of 67 PCs in surface water and groundwater have been published between 2000 and 2013 (see Table 4.3). The highest concentrations ($>200 \text{ ng L}^{-1}$) of PCs in surface water have been detected for paracetamol ($3.59 \times 10^3 \text{ ng L}^{-1}$), furosemide (605 ng L^{-1}), sotalol (504 ng L^{-1}), carbamazepine (345 ng L^{-1}), ofloxacin (306.1 ng L^{-1}), naproxen (264 ng L^{-1}), hydrochlorothiazide (255.8 ng L^{-1}), lincomycin (248.9 ng L^{-1}), Atenolol (241.9 ng L^{-1}), sulfadiazine (236 ng L^{-1}), ibuprofen (210 ng L^{-1}), salicylic acid (205 ng L^{-1}), and bezafibrate (202.7 ng L^{-1}) [185].

Relatively few substances have been analyzed in the Swiss aquatic environment or in wastewaters: several antibiotics [103, 186, 187] and anti-inflammatory drugs [188–191], one antiepileptic agent [191], and one metabolite of some blood lipid regulators [190, 192].

4.5.4 PCs in Seawater

Coastal water is considered the ultimate sink for sewage and other by-products of human activities. PCs in marine waters represent a threat to the aquatic environment, with effects such as acute and chronic toxicity to aquatic organisms, accumulation in the ecosystem, as well as threats to human health [193].

Thirteen PCs were detected in the coastal waters off south-western Taiwan. The results are summarized in Table 4.4. Among all the PCs studied, paracetamol, caffeine, and pseudoephedrine were detected in 100% of the samples [194].

A global comparison of selected PCs concentrations in seawater from America, Europe, and Asia is shown in Table 4.5.

4.5.5 PCs in Drinking Water

In 2012, the WHO published [24] a key document concerning PCs in drinking waters, their origin, occurrence, and fate. Studies in the United States have

Table 4.3 Concentration of selected drugs and TPs in groundwater.

Parent compound	TPs	Concentration (ng L ⁻¹)	References
Acetylsalicylic acid	Salicylic acid	1–620	[172, 174–176]
Atenolol	Atenolol-desisopropyl	6.4	[173]
Carbamazepine	2-Hydroxy-carbamazepine	5.5–48	[172]
	3-Hydroxy-	3.0–39.9	[172]
	10,11-Epoxy-	1.07–33.7	[172–174]
	10,11-Dihydro-10,11-dihydroxy-	15–20	[173]
	Acridone	0.9–8.2	[172]
	Acridin	4.5–15.8	[172]
Clofibrate	Clofibric acid	1.43–4210	[172, 177, 178]
Diazepam	Desmethyldiazepam	3.6–12.9	[172]
Diclofenac	4-Hydroxy-diclofenac	14.8–147	[172]
Enalapril	Enalaprilat	2.06–12.5	[172]
Erythromicin	Anhydroerythromycin	0.3–300	[105, 172]
Lamotrigine	Lamotrigine 2- <i>N</i> -glucuronide	17	[179]
Metamizol (dipyrone)	<i>N</i> -Acetyl-4-amino-antipyrine	1–362	[174, 180]
	<i>N</i> -Formyl-4-amino-	4.4–275	[173, 174, 180]
Nifedipine	Dehydro-nifedipine	22	[181]
Primidone	Phenyl-ethylmalonamide	50–540	[182]
Propanolol	4-Hydroxy-propanolol	5–21.4	[172]
Sulfadiazine	<i>N</i> -Acetyl-sulfadiazine	0.9–37.2	[172, 183]
Sulfamerazine	<i>N</i> -Acetyl-sulfamerazine	5–18	[183]
Sulfamethazine	<i>N</i> -Acetyl-sulfamethazine	0.02–57.0	[172, 183, 184]
Sulfamethoxazole	<i>N</i> -Acetyl-sulfamethoxazole	1.4–5.5	[172, 183]
	Desamino-	6.0	[177]
	4-Nitro-	4.1	[177]
Sulfapyridine	<i>N</i> -Acetyl-sulfapyridine	1.6–6	[183]
Venlafaxine	<i>N</i> -Desmethylvenlafaxine	1.5–3.9	[173]

detected very low levels of PCs in treated drinking water. The highest concentration reported was 40 ng L⁻¹ for meprobamate [107]. Studies have also found several PCs in tap water at concentrations ranging from ng L⁻¹ to low µg L⁻¹ in several countries in Europe, including Germany, the Netherlands, and Italy [195]. Between 15 and 25 PCs have been detected in treated drinking water worldwide, as reported in the literature [60, 107].

4.5.6 PCs in Soil

Studies concerning PCs in the terrestrial environment are less common than on those in the aquatic environment. However, in consideration of a comprehensive

Table 4.4 The 13 PCs detected in seawater in southwestern Taiwan.^{a)}

	Detected rate (%)	Concentration limits (ng L ⁻¹) ^{b)}
Paracetamol	100	2.6–16.7
Ampicillin	15	n.d.–88.7
Caffeine	100	1.24–16.92
Carbamazepine	7.7	n.d.–3.83
Cefalexin	73	n.d.–9.19
Codeine	98	n.d.–63.6
Erythromycin	17	n.d.–26.6
Gemfibrozil	39	n.d.–3.67
Ibuprofen	46	n.d.–12.1
Ketamine	27	n.d.–21.1
Ketoprofen	65	n.d.–23.3
3,4-Methylenedioxymethamphetamine (MDMA)	15	n.d.–4.82
Pseudoephedrine	100	0.71–2.65

a) Data taken from Ref. [194].

b) N.d. = not detected.

risk assessment these exposure routes should be equally taken into account; this is useful in particular for terrestrial ecosystems that depend on surface waters.

PCs, like their parent compounds or metabolites, enter agricultural land when digested sludge, which is retained in WWTPs, when applied as fertilizer. Hence, sludge acts as a sink for sludge-associated PCs [196].

When manure is used as fertilizer, veterinary PCs are more likely to directly contaminate the soil, and the runoff reaches rivers. Runoff, as a diffuse input of PCs compared to point sources like WWTPs, is more difficult to monitor, but it appears to be a major discharge path for the pollution of surface waters, particularly in agricultural areas [43].

In some countries (e.g., Switzerland), sludge is routinely combusted, but incorrect deposition before combustion can lead to leachates of certain PCs, which may enter the aquatic environment [197]. Countries of the EU (e.g., Germany), or the North American continent (e.g., Canada), use sludge as a fertilizer for arable farmland [198], whereupon runoff from fields may feed micro-pollutants to streams and lakes during heavy rain events.

Generally, the concentrations of PCs detected in the soils are quite low when compared with that of PCs in water resources. The six most common PCs found in soil in different countries are shown in Table 4.6 [175, 199–202]. They are the antibiotics ABs (trimethoprim, sulfadiazine, and triclosan), analgesics (ibuprofen and diclofenac) and antiepileptic (carbamazepine).

Table 4.5 Global comparison of CEC concentrations (ng L⁻¹) in seawater.^{a)}

Compound	Asia				Europe				America	
	Taiwan		China	Hong Kong	Vietnam	UK	Belgium	Norway	Germany	USA
	Southwestern coast	Northern coast								
Paracetamol	2.6–16.7					n.d.				n.d.–11
Diclofenac	n.d.	n.d.–53.6	n.d.–32.7			n.d.–195	n.d.	n.d.	n.d.–6.2	n.d.–0.6
Ibuprofen	n.d.–12.1	n.d.–57.1	n.d.–31.1			n.d.–755		n.d.–0.7	n.d.–0.6	n.d.–30
Ketoprofen	n.d.–23.3	n.d.–6.59	n.d.				n.d.		n.d.	
Naproxen	n.d.		n.d.–5.4							n.d.–26
Salicylic acid	n.d.		n.d.–143				n.d.–855			
Codeine	n.d.–63.6									
Sulfamethoxazole	n.d.		0.3–56.8	0.6–47	4.0–23	n.d.	n.d.–96			n.d.–3.4
			2.1–50.4							
Ampicillin	n.d.–88.7									
Tetracycline	n.d.		n.d.–2.37	n.d.–122						
				13–313						
Erythromycin	n.d.–26.6		0.05–45.4	9.5–486	9.0–12	n.d.				
			0.56–25.2	4.7–1730						
Cefalexin	n.d.–9.19			n.d.–182						
				6.1–504						
Clofibric acid	n.d.	n.d.–55.1	n.d.–18.3			n.d.–111	n.d.	n.d.	n.d.–18.6	
Gemfibrozil	n.d.–3.67		n.d.–7.7							
Carbamazepine	n.d.–3.83		n.d.–25.5				n.d.–321	n.d.		n.d.–0.9
Caffeine	1.24–16.9							7.0–87	2.0–15	n.d.–44.7
Atenolol	n.d.						n.d.–293			n.d.–11
Ketamine	n.d.–21.1									
Pseudoephedrine	0.71–2.65									
MDMA	n.d.–4.82									

a) Data taken from Ref. [194]. n.d. = not detected.

Table 4.6 Concentration of selected PCs found in soil in different countries.^{a)}

Compound	Country, region	Range of concentration ($\mu\text{g kg}^{-1}$) ^{b)}	References
Carbamazepine	Mexico	2.6–7.5	[199]
	Hebei, China	0.02–0.06	[175]
	USA	n.d.	[200]
	USA	0.7–1.4	[201]
Trimethoprim	USA	n.d.–0.64	[200]
	Hebei, China	0.64–2.15	[175]
	Malaysia	3.1–60.1	[202]
Ibuprofen	Mexico	n.d.–0.1	[199]
	Hebei, China	1.51–5.03	[175]
Diclofenac	Mexico	n.d.	[199]
	Hebei, China	0.35–1.16	[175]
Sulfadiazine	Hebei, China	1.15–3.82	[175]
	Malaysia	n.d.	[202]
Triclosan	USA	n.d.	[201]
	Mexico	n.d.–16.7	[199]

a) Data taken from Ref. [73].

b) n.d. not detected.

4.6 Ecotoxicological Aspects of PCs on Environment

The pollution of the environment by pharmaceutical residues in mixtures is an area of increasing concern, with various open questions concerning their adverse effects on non-target organisms [203].

The continuous consumption of drugs even at sub-therapeutic concentrations represents a potential threat to public health, although it should be borne in mind that it is still impossible to evaluate the effects of exposure on human health [204, 205]. In addition, many non-target organisms (which possess human- and animal-like metabolic pathways) are therefore inadvertently exposed to active substances released into the environment [206]. Nevertheless, there are currently no legally regulated maximum permitted concentrations of PCs in the environment, despite their unknown impact on the environment and human health. A comprehensive manner to evaluate the toxicity effects on non-target organisms must include the development of specific tests embracing either acute effects or chronic effects.¹⁰ In the latter, effects are measured through specific parameters such as growth index or reproduction rates [207, 208].

The presence of PCs in the environment raises concerns about their possible bioaccumulation and biomagnifications within the food web. Recently, the WHO

¹⁰ By means of exposure to different concentrations of a chemical compound over a prolonged period of time.

released a report and information sheet on the current state of the science on PCs with recommendations for guidelines and future research priorities. A work group of experts in a report on water treatment and quality, toxicology, and water policy, concluded that at currently detected concentrations and predicted exposure levels, PCs do not pose a serious risk to human health.

It is important to recognize that detection of these compounds does not directly correlate to human health risks that could be verified by available human risk assessment methods. In addition, there is currently no standardized practice or protocol for the sampling and analytical determination of PCs in water or any other environmental media that ensures the comparability and quality of the data generated. [24]

Acute toxicity data is valuable only when accidental discharge of the drugs occurs, since the environmental concentrations usually reported for these compounds are low. Bioaccumulation and chronic toxicity tests are scarce [206] probably due to the complex experimental work involved [208].

The Organization for Economic Co-operation and Development (OECD) guidelines for the testing of chemicals) are frequently used for risk assessment of PCs in the environment, and their results are used for informing the public about potential environmental effects. However, PCs are different from other aquatic contaminants, as their pharmacological effects occur at concentrations much lower than concentrations that may be toxic. This introduces a conceptual dilemma, as pharmaceutical contaminants, at least in theory, have the capacity to improve fitness of the exposed individuals, but the tests used for risk assessment are designed to measure harmful effects. Indeed, the need for using new approaches that focus on the pharmacological effects for risk assessment has been highlighted [209, 210], but the bias toward harmful effects have never been discussed [211]. There is an obvious reason why pharmacological effects that improve the health of organisms is not detected in the way risk assessments are currently conducted; ecotoxicological tests strive to have no mortality in the control treatment and tests with mortalities $\geq 10\%$ are disregarded.

The consumption of PCs is very high and therefore Europe and the recent Directive 2013/39/EC [212] on the review of priority substances in surface water bodies has included three PCs (diclofenac, EE2, E2) of widespread use in the European monitoring list, the so-called watch list.

The load of PCs in the WWTPs is comparable to agrochemicals but compared to pesticides the same requirements and tests have not been applied so far [213] to assess the environmental impacts.

Upon discharge into the environment most PCs end up in the aquatic domain where they settle in the sediments and play a role in exposing aquatic organisms. PCs may become persistent in the environment because of their continual influx from many routes into the environment [38]. Their continuous influx compensates for their transformation and removal rates and may lead to chronic exposure of aquatic organisms [38].

PCs are metabolized in living organisms and they suffer natural attenuation processes such as adsorption, dilution, or degradation in the environment,

depending on some physicochemical properties such as their hydrophobicity, solubility or acidity or thermal stability that condition their biodegradability. An added problem is that sometimes, the fate of these is hazardous, too, for the environment, because the transformation, for example, by human metabolism of some of these chemicals can also be considered toxic. The most relevant therapeutic classes in terms of environmental contamination are presented in Figure 4.4 [208].

According to the scientific literature, most research on the effects of PCs on biological systems has been conducted so far using only one PC at a time (see Table 4.7 [11]. However, PCs do not occur only as isolated, pure substances in the environment.

Exposure to multiple chemicals, including PCs may result in a synergic effect called the “cocktail effect.” Current regulatory approaches to chemicals are usually based on evaluating the effect on living beings and ecosystems of single substances. In 2012, the European Commission reported a communication on the combined effects of chemical mixtures. According to detected concentrations of PCs, it becomes an important goal to evaluate long-term effects on the environment of multiple molecules with biological activity [220].

Guidelines on mixtures by the WHO and USEPA are already available, but they focus on the possible adverse effects on human health only. The scientific and regulatory current status concerning the toxicity of chemical mixtures is discussed in the literature, highlighting the necessity of developing relevant guidelines for assessing mixture toxicity. This has led the European Commission to publish a communication on the combined effects of PCs [220].

It is important to note that the number of active pharmaceutical ingredients is continuously increasing [221]. The importance of studying the effects of mixtures rather than of single PCs is evident [222].

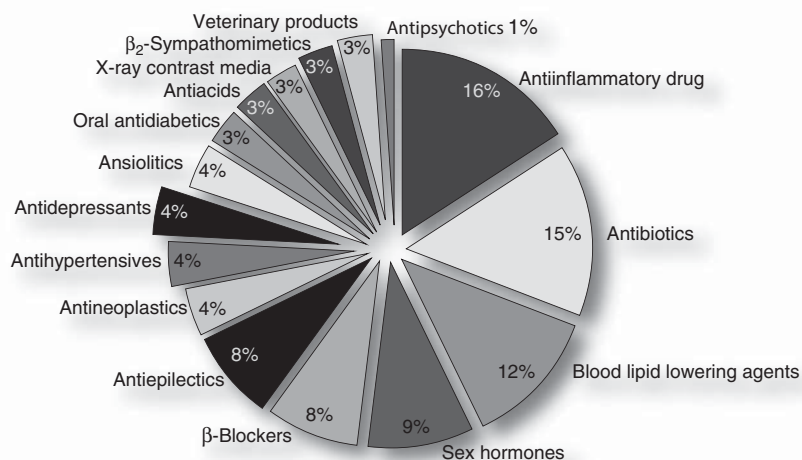


Figure 4.4 Relative percentage of therapeutic classes detected in the environment [208].

Table 4.7 Toxic and ecological effects of PCs on organisms.^{a)}

Compounds	Organism	Type of risks involved (exposure level)	References
Diclofenac	Fish	Tubular necrosis in the kidney and hyperplasia and fusion of the villi in the intestine at 1 $\mu\text{g L}^{-1}$ (0, 0.5, 1, 5, and 25 $\mu\text{g L}^{-1}$)	[214]
		Both renal lesions and alterations of the gills occurred at 5 $\mu\text{g L}^{-1}$ (1–500 $\mu\text{g L}^{-1}$)	[215]
		Effects on hepatic gene expression (1–500 $\mu\text{g L}^{-1}$)	[216]
Ibuprofen	Algae	Proteomic analysis showed effects in chloroplasts (92 and 920 ng L^{-1})	[217]
Carbamazepine	Algae	Proteomic analysis showed effects in chloroplasts (150 mg L^{-1})	[217]
Sulfamethoxazole	Algae	Chronic toxicity effects for the photosynthetic apparatus (0–2500 $\mu\text{g L}^{-1}$)	[218]
17 α -Ethinylestradiol	Fish	Brain and inter-renal steroidogenic acute regulatory protein and cytochrome P-450-mediated cholesterol side-chain cleavage expressions (5–50 ng L^{-1})	[219]

a) Data taken from Ref. [73].

4.7 Removal of PCs

The removal of PC residues in municipal WWTPs is a major challenge in reducing the emission of micro-pollutants to the aqueous environment. As “the activated sludge process” has been the most common unit operating in municipal WWTPs, the majority of research on treatability of PCs in WWTPs is focused on this process and its relative efficiency [223].

The amounts of various PCs detected in inlet and outlet water of various WWTPs confirmed that many of these substances are not effectively removed by these treatments. More effective and specific treatments are required to reduce the environmental and potential impact of these pollutants. Among these treatments, both adsorption on activated carbons and advanced oxidation/reduction processes are under research and have yet to be applied on an industrial scale [224].

The main purpose of drinking-water treatment plants DWTPs in the past was to remove natural organic matter, hardness, and microorganisms from the target source. As the presence of PCs in drinking water has lately been a significant health concern, elimination of such pollution has now become a major challenge, particularly if the source is effluent-dominated surface water [223]. Fortunately, a conventional coagulation process that is a counterpart of most DWTPs, can effectively remove PCs with $\log K_{ow} > 5$ [225].

Early studies regarding the treatment of hospital wastewater by physicochemical processes, such as advanced oxidation processes, nanofiltration, reverse osmosis, and powdered activated carbon adsorption, have been reported [226–229].

4.7.1 Conventional Systems for Removing PCs in Water-Treatment Systems

STPs can be equipped with primary, secondary, and tertiary treatment steps (see Chapter 2). WWTPs comprise a primary system of physicochemical treatments (involving the removal of large objects, floating solids, and suspended solids from raw sewage) and a secondary system that consists of a biological reactor formed by activated sludge. The activated-sludge process makes use of biological sludge infested with microorganisms often combined with bubbling air or oxygen to reduce the organic content from the sewage [230]. The tertiary process removes pollutants not adequately removed by the secondary treatment, particularly nitrogen and phosphorus, often accomplished by some means of chemical treatment, sand filters, or other methods. During the tertiary treatment, microorganisms such as pathogens and viruses should also be removed by disinfection [231]. These conventional plants have a limited capacity to remove pharmaceutical products from urban wastewaters. WWTPs are not designed to remove these contaminants and, therefore, many of them pass unchanged and reach the surface water [138].

WWTPs in Spain usually comprise only primary and secondary treatments, with the latter based on conventional activated sludge, whereas tertiary treatments are seldom applied [232]. On the contrary, most European WWTPs do include tertiary treatment. In some cases, advanced oxidation technologies have been investigated for the elimination of PCs by the use of ozone [233], different chemical oxidants [234], and sonolysis [235]. Some studies have considered the effect of UV radiation in the removal of some of these agents (mainly analgesics, antiarrhythmia drugs, and antibiotics) and concluded that UV was not effective enough for the quantitative removal of the PCs studied from water [236–239].

The first treatment of raw water consisted of preoxidation with chlorine. The use of chlorine is still the most widespread conventional treatment for disinfecting drinking waters. ClO_2 is a more potent oxidant than Cl_2 and can degrade numerous organic compounds by oxidation.

Coagulation with alum-coagulants, flocculation with a diallyldimethyl ammonium chloride homopolymer (poly-DAD-MAC), and clarification through sand filters did not achieve extensive reductions of PCs concentrations [195].

According to Heberer [169], of the most commonly used analgesics, WWTPs can eliminate paracetamol, acetylsalicylic acid, and ibuprofen but are not effective in removing diclofenac. With regard to antibiotics, penicillins readily hydrolyze in water and tetracyclines precipitate with cations such as Ca^{2+} , accumulating in treatment-plant sludge [38].

In a study by Huerta-Fontela *et al.* [195] 35 of 55 drugs were detected in the raw water with concentrations up to 1200 ng L^{-1} . The complete treatment accounted for the total removal of all the compounds detected in raw waters except for five

of them. Phenytoin, atenolol and hydrochlorothiazide were the three PCs most frequently found in treated waters at concentrations of about 10 ng L^{-1} .

4.7.2 Adsorption on Activated Carbon

The use of activated carbon to adsorb contaminants from PCs (mainly aromatic compounds) has been recently studied. The main advantage of using activated carbon to remove PCs is that it does not generate toxic or pharmacologically active products. According to the literature, activated carbons generally demonstrated a high capacity to adsorb PCs, depending on the activated carbon type, pharmaceutical composition, and solution chemistry [224].

There have been numerous studies on the adsorption of aromatic compounds in aqueous solution, but the underlying mechanisms must be established to enhance the effectiveness of this process to remove these contaminants.

4.7.3 Technologies Based on Advanced Oxidation Processes (AOPs)

AOPs are very effective in the oxidation of numerous organic and inorganic compounds. These processes are all based on the *in situ* generation of very powerful oxidizing agents such as the free radicals ($\text{HO}\cdot$, $\text{O}_2^{\cdot-}$, $\text{HO}_2\cdot$) [240]. The hydroxyl radical ($\text{HO}\cdot$) is nonselective and a highly reactive species that can successfully react with most organic compounds to convert them into less complex and less harmful intermediates [223]. Advanced oxidation processes are a viable option for destroying PC residues in WWTP and DWTPs effluents.

4.7.3.1 AOPs Based on Ozone

An oxidation process with ozone (O_3) has been demonstrated to be one of the most effective disinfection techniques for the removal of PCs. Water treated with ozone was passed through 20 granular activated filters of 150 m^3 each.¹¹ The final step of the process on the DWTPs consisted of a post-chlorination [195]. Only five PCs out the 55 selected in a study by Huerta-Fontela *et al.* [195] survived treatments and were found at trace levels in the treated waters.

4.7.3.2 AOPs Based on UV Radiation

The excellent capacity of hydroxyl radicals to oxidize organic compounds has led to research on their photochemical generation. Collado *et al.* [131] studied the occurrence and removal of 81 representative PCs in a municipal WWTP located in a highly industrialized area, with partial water reuse after UV tertiary treatment and discharge into a Mediterranean river. Water monitoring was performed at different points in the WWTP and river over three seasons. Consistent differences between therapeutic classes were observed in terms of influent concentration, removal efficiency, and seasonal variation. Conventional (primary and secondary) treatment was unable to completely remove numerous compounds and UV-based tertiary treatment played a complementary role for some of them. Some results of this study are shown in Table 4.8.

¹¹ Adsorption on activated carbon.

Table 4.8 Concentration (ng L⁻¹) of PCs in the influent and effluent of WWTP and in the inlet and outlet of the UV treatment.^{a)}

Compound	Influent	Effluent	Inlet	Outlet
Atenolol	2,224	274	282	184
Atorvastatin	97 ^{b)}	9 ^{b),c)}	10 ^{b),c)}	3 ^{b),c)}
Azithromycin	129	143	153	115
Bezafibrate	121 ^{b)}	3 ^{c)}	8 ^{c)}	12
Carbamazepine	27 ^{b)}	49 ^{b)}	54 ^{b)}	47 ^{b)}
Ciprofloxacin	392	176	178	137
Citalopram	95 ^{b)}	50	43	36
Clarithromycin	100	99	87	77
Codeine	81	60	63	49
Diclofenac	288 ^{b)}	309	286	154
Erythromycin	15 ^{b)}	18	17 ^{b)}	15
Furosemide	1901	288	358	271
Gemfibrozil	1009	184	173	115
Hydrochlorothiazide	1370	1036	1075	622
Ibuprofen	10,751	28 ^{b),d)}	n.d. ^{b)-d)}	n.d. ^{b)-d)}
Indomethacine	45 ^{b),d)}	61 ^{d)}	61 ^{d)}	47 ^{d)}
Irbesartan	281	246	230	205
Ketoprofen	506 ^{c)}	146 ^{b)}	144 ^{b)}	110 ^{b)}
Levamisole	24 ^{b)}	45	50	41
Losartan	211	162	151	128
Meloxicam	916 ^{b)}	325 ^{b)}	318 ^{b)}	125 ^{b)}
Metoprolol	393	169	184	110
Nadolol	27 ^{c)}	18 ^{c)}	5 ^{b),c)}	n.d. ^{b)-d)}
Naproxen	7661	247	227	157
Ofloxacin	128	118	164	99
Paracetamol	12,955	40 ^{d)}	29 ^{d)}	23 ^{d)}
Paroxetine	592 ^{c)}	179 ^{c)}	190 ^{c)}	62 ^{c)}
Phenazone	26 ^{b),d)}	10 ^{b)}	13 ^{b)}	7 ^{b)}
Piroxicam	325	225	212	177
Ranitidine	1165	176	170	113
Salicylic acid	6593	65 ^{b)}	107 ^{b)}	6 ^{b)}
Sulfamethoxazole	70 ^{b),d)}	10 ^{b),d)}	11 ^{b),d)}	12 ^{b),d)}
Tenoxicam	325 ^{b)}	238 ^{b)}	216 ^{b)}	169 ^{b)}
Thiabendazole	n.d. ^{b),d)}	4 ^{b),c)}	4 ^{b),c)}	1 ^{b),c)}
Iopromide	62 ^{b),c)}	195 ^{b)}	489 ^{b),c)}	106 ^{c)}
Trazodone	75 ^{b)}	39 ^{b)}	41 ^{b)}	24 ^{b)}

(Continued)

Table 4.8 (Continued)

Compound	Influent	Effluent	Inlet	Outlet
Trimethoprim	54 ^{b)}	7 ^{b)}	5 ^{b)}	1 ^{b),d)}
Valsartan	1511	99	92	62
Venlafaxine	4108	2659	2488	1806
Xylazine	58 ^{b),c)}	31 ^{b),c)}	30 ^{b),c)}	7 ^{b),c)}

- a) Data taken from Ref. [131]; for the calculations, the non-detected compounds were considered as zero and halves of method quantification limit (MQL) values were applied for the compounds at concentration <MQL ($n = 3$).
- b) Not present in the winter sampling campaign.
- c) Not present in the summer sampling campaign.
- d) Not present in the spring sampling campaign.

4.7.3.3 AOPs Based on γ -Radiation

Radiolysis is based on the generation of radicals, highly reactive electrons, ions, and neutral molecules through the exposure of water to high-energy electromagnetic radiation [241, 242].

4.7.3.4 Electro-Oxidation with and without Active Chlorine Generation

The most widely used electrochemical technique for wastewater remediation is the electrochemical oxidation, frequently called anodic oxidation when non-chloride solutions are treated.

4.8 Conclusions

PCs are among the contaminants with the highest input into the environment due to their extraordinary consumption. Until now, PCs have not been included in the list of priority substances regulated by the European Parliament Directive 2008/105/EC [243], which defines maximal tolerated concentration in inland and other surface water and thus, no environmental-quality standards have been stipulated for them.

PCs constitute the most investigated group of wastewater-derived CECs in the environment. However, as in the case of pesticides, less consideration is given to pharmaceutical TPs and human metabolites than to parent compounds in monitoring studies. Of all the aspects of PCs in the environment, the one that is perhaps the best developed is chemical identification and quantitation. There are different sources for PCs in the environment. The major sources of PCs in the environment are primarily STW effluent and, secondarily, terrestrial runoff. Veterinary PCs reach the aquatic environment by infiltrating the soil and reaching an aquifer, or by surface runoff. Probably, the main source for PCs used by humans is the excretion [203], but unused PCs may also reach the aquatic environment.

The occurrence of a multitude of different drugs in rivers and streams indicates the relatively high stability of these medicinal compounds under environmental conditions. Clearly, the common sewage treatment process is insufficient to completely eliminate these drug residues.

Microbial TP's of PC's can be formed during biological wastewater treatment, from contact with sediment and soil, and during bank filtration. Further, TP's can be formed by UV irradiation in surface waters and during oxidative treatment processes.

Some PC's (e.g., blood-lipid regulators such as clofibric acid, X-ray contrast media) are ubiquitous and extremely persistent in the environment. The low volatility of PC's means that their distribution through the environment occurs primarily through aqueous transport and food-chain dispersal. The polar, nonvolatile nature of most drugs prevent their escape from the aquatic realm. Many PC's are bio-transformed by organisms such as bacteria and fungi in the environment [244, 245].

Some PC's show very high acute aquatic toxicity, and recent evidence shows that drugs have effects on the environment (estrogens and their effects on fish and the effects of diclofenac on vultures) at extremely low concentrations. Structural transformations may also be a result of effluent treatment [59, 246–250].

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5

Therapeutic Classes of PCs in the Environment

5.1 Introduction

Pharmaceuticals (PCs) are synthetic or natural chemicals that can be found in prescription medicines, over-the-counter therapeutic drugs, and veterinary drugs, and they contain chemicals that evoke pharmacological effects and confer significant benefits on society. PCs do not consist of a consistent group of substances with similar chemical, structural, biological, or toxicological properties. Rather, PCs can be classified according to their purpose and biological activity (e.g., ABs, analgesics, antineoplastics, anti-inflammatory substances, antihistamines, X-ray contrast media, etc.). In this sense, PCs can be analyzed according to their classification in therapeutic classes (see Table 5.1). These classes were determined by the Anatomic Therapeutic and Chemical (ATC) classification proposed by the WHO Collaborating Center for Drug Statistics Methodology.¹

The classification of PCs by their chemical structure is used mainly in the analysis of active substances within subgroups of medicines, for example, within the group of ABs subgroups such as β -lactams, cephalosporins, penicillins, or quinolones. In these subgroups, the compounds might be expected to have similar chemical behavior.² However, even minor changes in the chemical structure may have a significant impact on other properties that govern their environmental fate [1].

The different classes of drugs will be covered taking into account this classification and environmental detection. The therapeutic groups most commonly detected in water are [2]:

In Table 5.2 the minimum and maximum concentrations of some PC classes are shown.

- Antibiotics (tetracyclines, macrolides, β -lactams, penicillins, quinolones, sulfonamides, fluoroquinolones, chloramphenicol, and imidazole derivatives).
- Estrogens and hormonal compounds.

1 WHO Collaborating Centre for Drug Statistics Methodology, 2011. Guidelines for ATC classification and DDD assignment. Oslo, 2010.

2 Closely related chemical structures may be accompanied by identical or at least a similar mode of action.

Table 5.1 Classes and codes of anatomic therapeutic.

Code	Classes	Code	Classes
A	Alimentary tract and metabolism	L	Antineoplastic and immunomodulating agents
B	Blood and blood forming organs	M	Musculo-skeletal system
C	Cardiovascular system	N	Nervous system
D	Dermatologicals	P	Antiparasitic products, insecticides, and repellents
G	Genito-urinary system and sex hormones	R	Respiratory system
H	Systemic hormonal preparations, excluding sex hormones and insulins	S	Sensory organs
J	Anti-infectives for systemic use	V	Various

Table 5.2 Range and typical concentrations (ng L⁻¹) detected for main PC classes.^{a),b)}

Therapeutic classes	Influent		Effluent	
	Range	Typical	Range	Typical
Non-steroidal anti-inflammatory drugs (NSAIDs)	22,365–50,584	50,894	1298–2575	1298
Psychiatric drugs	2403–9833	2455	819–5803	819
Histamine receptors	290 –2597	608	118–259	118
Lipid regulators	1000–1398	1283	76–300	212
β-Blockers	1706–4145	4145	196–803	196
Diuretic	2689–3658	3466	539–2083	539
Anti-hypertensives	1379–2823	1379	164–1055	164
ABs	677–1,185	677	307–1062	335
X-ray contrast agent	n.d.–186	186	n.d.–573	573
Anthelmintics	n.d.–48	48	33–68	46
Sedation drugs	n.d.–174	174	n.d.–92	92
Total		65,315		4392

a) Data taken from Ref. [4], from three sampling campaigns.

b) n.d. = not detected.

- Anti-inflammatories and analgesics (paracetamol, acetylsalicylic acid, ibuprofen, and diclofenac).
- Antidepressants (benzodiazepines).
- Antiepileptics (carbamazepine).
- Lipid-lowering drugs (fibrates).
- β-Blockers (atenolol, propanolol, and metoprolol).
- Antiulcer drugs and antihistamines (ranitidine and famotidine).
- Other substances (cocaine, barbiturates, methadone, amphetamines, opiates, heroin, and other narcotics) [3].

Metabolites as well as environmental TPs, together with parent PCs, pose threats to the aquatic and terrestrial environment. Some of these undesirable environmental effects caused by residual PCs, especially in waters, are classified based on three main groups: ABs, endocrine-disrupting PCs, and psychotropic drugs.

5.2 Antibiotics (ABs)

Traditionally, ABs are defined as chemical compounds that eradicate or inhibit the growth of other microorganisms [5]. However, the term “antibiotic” has been expanded for antibacterial, antiviral, antifungal, and antitumor compounds. Most of these substances have a microbial origin, but they may also be semi-synthetic or totally synthetic. ABs can be divided into several classes, according to different criteria: spectrum, action mechanism, and chemical structure.

ABs are molecules used in medical treatment against bacterial and fungal infections. There are two main mechanisms for infection control: the first one causes bacterial cell death and the second one restricts growth and reproduction. The emergence of ABs has meant an enormous advance in human capability to control many previously fatal diseases. The first ABs that were used commercially in the 1930s were sulfonamides. Since then, many families of new ABs have been developed or synthesized. Figure 5.1 depicts the timeline for the main families of ABs commonly used against most infections.

In the late 1930s, natural and synthetic ABs were introduced and their use in medical treatment for humans and livestock has increased. According to their environmental interaction ABs are considered “pseudo-persistent,” which means they enter the environment continuously, resulting in permanent presence.

5.2.1 Chemical Classes of Antibiotics

ABs can be divided into several classes according to different criteria: origin (microbial, semisynthetic, synthetic), spectrum, mechanism of action, and chemical structure (see Figure 5.2). ABs with similar chemical structures or within a structural class generally exhibit similar activity, spectra, and toxicity. ABs can be classified on the basis of their chemical structure into different classes that are listed as follows [5, 6]:

Aminoglycosides: These consist of one or more amino sugars joined by a glycosidic linkage to an aminocyclitol nucleus of the drug (e.g., amikacin, netilmicin, neomycin, gentamicin, kanamycin, streptomycin, tobramycin) (see Figure 5.3).

Ansamycins: These are complex macrocyclic antibiotics (e.g., rifampin or rifampicin, geldanamycin, rifamycins, and naphthomycin) (see Figure 5.4).

Tetracyclines: These antibiotics contain an octahydronaphthacene ring skeleton, consisting of four fused rings (e.g., tetracycline, doxycycline, limecycline, chlortetracycline, minocycline, oxytetracycline) (see Figure 5.5).

Anthracyclines: These are structurally glycosylated tetracyclines.

β-Lactams: Can be divided into three subclasses:

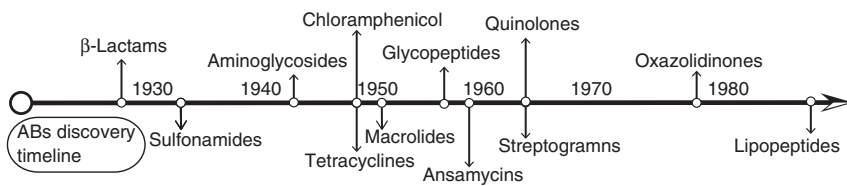


Figure 5.1 Timeline of the discovery of ABs.

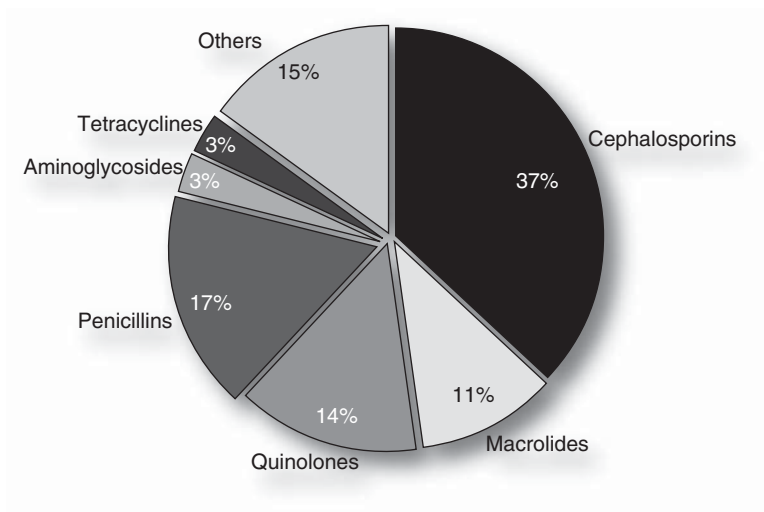


Figure 5.2 Abundance of ABs.

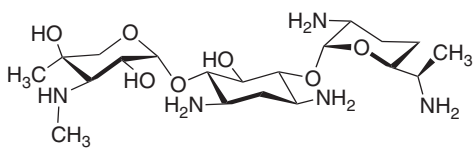
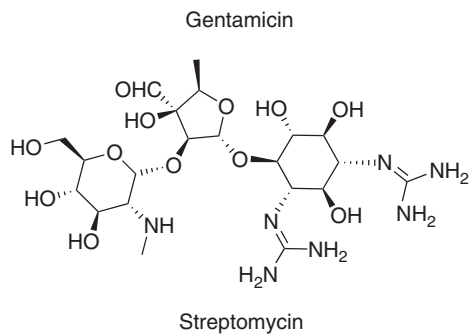


Figure 5.3 Chemical structure of aminoglycosides gentamicin and streptomycin.



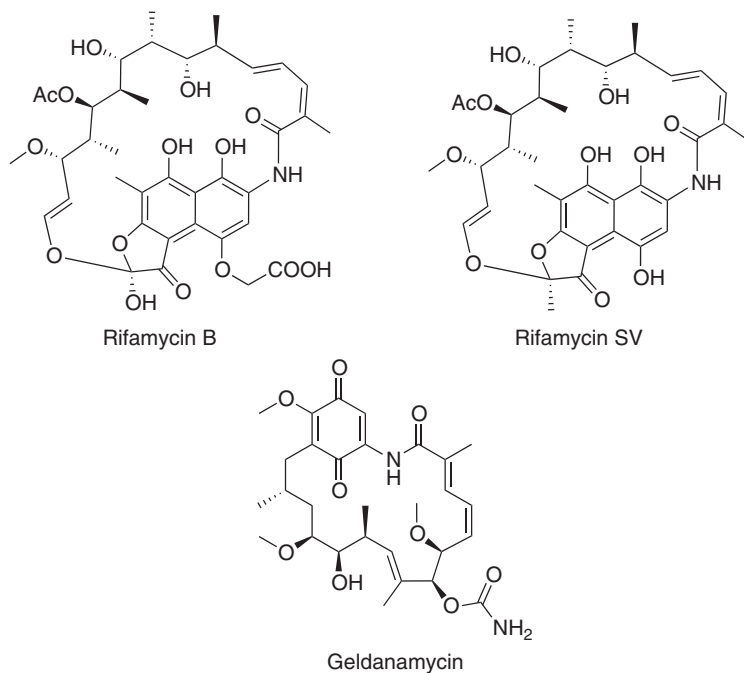
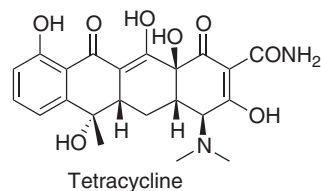


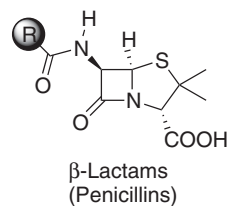
Figure 5.4 Chemical structure of common ansamycins.

Figure 5.5 Chemical structure of tetracyclines.



- **Penicillins:** Consist of a thiazolidine ring connected to a β -lactam ring, to which a side chain is attached (e.g., penicillin, ampicillin, amoxicillin, ticarcillin, methiin, and flucloxin) (see Figure 5.6).
- **Carbapenems:** These are structurally very similar to penicillins, but the sulfur atom of the structure has been replaced by a carbon atom (e.g., carbapenem, loracarbef).
- **Monobactams:** In these compounds, the β -lactam ring is alone and not fused to another ring (e.g., aztreonam, monobactam).

Figure 5.6 Chemical structure of penicillins (β -lactams).



Cephalosporins: These possess a cephem nucleus to which two side chains are linked: one the esterified carbamate group (R_2) and the other being linked to the nucleus (R_1) (e.g., cefapirin, cefaclor, cefixime, and cephalexin) (see Figure 5.7).

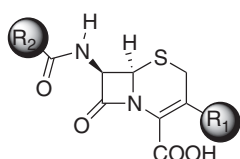
Chloramphenicol: This contains a nitrobenzene moiety connected to a propanol group as well as an amino group binding a derivative of dichloroacetic acid (see Figure 5.8).

Cyclic peptides: Vancomycin, streptogramins, polymyxins (see Figure 5.9).

Glycopeptides: These are composed of carbohydrate moieties (glycans) covalently attached to the side chains of an amino acid, for example, vancomycin, and teicoplanin (see Figure 5.10).

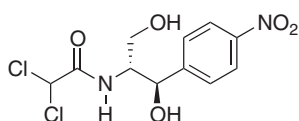
Imidazoles: These are heterocyclic compounds of five-membered di-unsaturated ring structure with two nitrogen atoms at nonadjacent positions, for example, azomycin, nimorazole, tinidazole and metronidazole (see Figure 5.11).

Lincosamides: They are a small family of antibiotics that have carbohydrate-type structures (e.g., lincomycin, lindamycin, clindamycin) (see Figure 5.12).



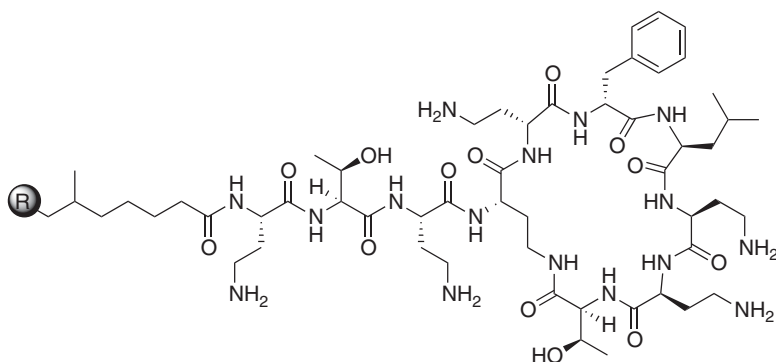
Cesphalosporins

Figure 5.7 Chemical structure of cesphalosporins.



Chloramphenicol

Figure 5.8 Chemical structure of chloramphenicol.



Polymyxin B1 ($R = H$)
Polymyxin B2 ($R = CH_3$)

Figure 5.9 Chemical structure of cyclic peptides polymyxin B1 and B2.

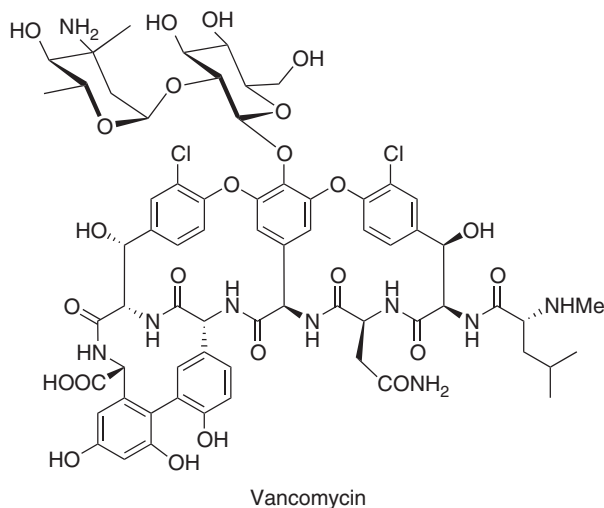


Figure 5.10 Chemical structure of glycopeptide vancomycin.

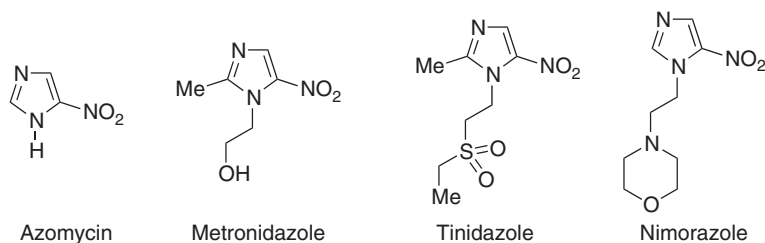
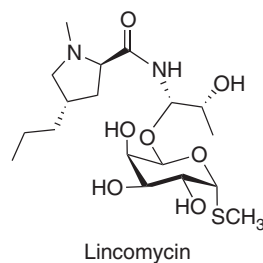


Figure 5.11 Chemical structure of imidazoles.

Figure 5.12 Chemical structure of lincosamide lincomycin.



Lipopeptides: A lipopeptide is a molecule consisting of a lipid connected to a peptide. Certain lipopeptides such as daptomycin are used as antibiotics (see Figure 5.13).

Macrolides: These are highly substituted monocyclic lactones. The lactone rings are usually 12, 14, or 16-membered, with one or more deoxy sugars glycosidically attached to hydroxyl groups, for example, erythromycin, clarithromycin, azithromycin, roxithromycin (see Figure 5.14).

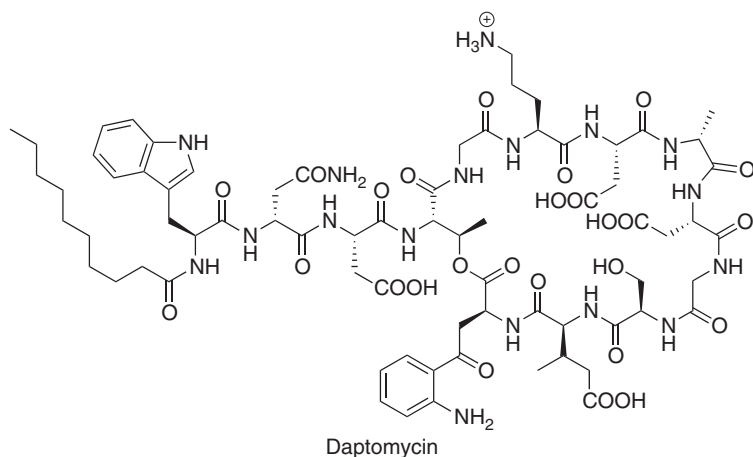


Figure 5.13 Chemical structure of lipopeptide daptomycin.

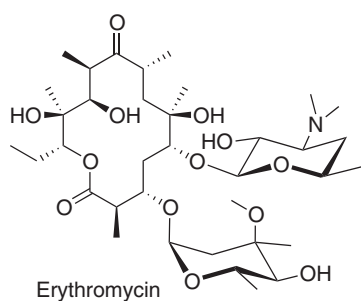


Figure 5.14 Chemical structure of erythromycin (macrolides).

Mitomycins: These have a unique chemical structure, in which three different functional groups (e.g., aziridine, carbamate, and quinone) are arranged around a pyrro[1,2-a]indole nucleus (e.g., mitomycin C) (see Figure 5.15).

Nitrofurans: Examples of these are furazolidone and nitrofurantoin (see Figure 5.16).

Oxazolidinones: These antibiotics are considered a choice of last resort where every other antibiotic therapy has failed, for example linezolid, tedizolid, posizolid (see Figure 5.17).

Polyenes: Composed by a conjugate alkene chain such as amphotericin B (see Figure 5.18).

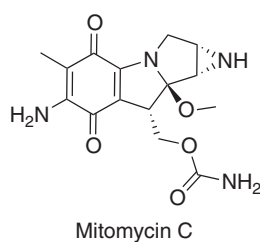


Figure 5.15 Chemical structure of mitomycin C.



Figure 5.16 Chemical structure of nitrofurans.

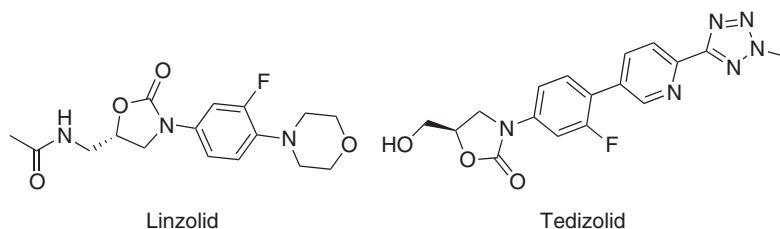


Figure 5.17 Chemical structure of oxazolidinones linezolid and tedizolid.

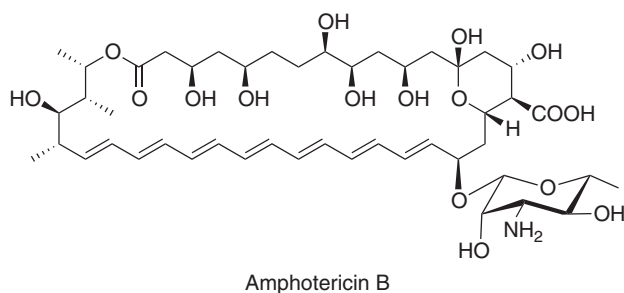
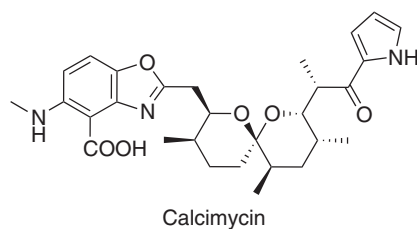


Figure 5.18 Chemical structure of polyene amphotericin B.

Polyethers: These are characterized by multiple tetrahydrofuran and tetrahydropyran rings connected by aliphatic bridges, direct C–C linkages, or spiro linkages. Other features include a free carboxyl function, many lower alkyl groups, and a variety of functional oxygen groups (e.g., calcimycin) (see Figure 5.19).

Polypeptides: These are polymers formed from the linkage of α -amino acids (e.g., bacitracin) (see Figure 5.20). Antimicrobial peptides are generally between 12 and 50 amino acids.

Figure 5.19 Chemical structure of polyether calcimycin.



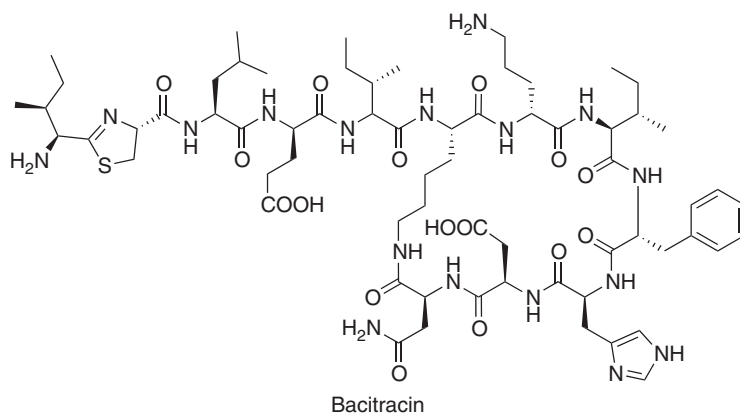


Figure 5.20 Chemical structure of polypeptide bacitracin.

Quinolones: Their structure contains two fused rings with a carboxylic acid and a ketone group. Most of the quinolones in clinical use are fluoroquinolones, having $-F$ attached to the central ring system, at the C_6 or C_7 positions, (e.g., ciprofloxacin, levofloxacin, nalidixic acid, trovafloxacin) (see Figure 5.21).

Quinoxaline derivatives: Their structure contains a benzene ring and a pyrazine derivative ring (e.g., carbadox) (see Figure 5.22).

Streptogramins: Antibiotic drugs used to treat hospital-acquired infections when no other antibiotic is effective (e.g., quinupristin, dalfoprisin, pristinamycin, and virginiamycin) (see Figure 5.23).

Sulfonamides: They are characterized by sulfonyl group connected to an amine group (sulfamide) (e.g., sulfisoxazole, sulfanilamide, prontosil, sulfadiazine) (see Figure 5.24). Sulfanilamide is the basic chemical structure.

Thiamphenicol: The $-NO_2$ group in chloramphenicol is changed by CH_3SO_2-

Trimethoprim: It is a diaminopyrimidine, a structural analog of the pteridine moiety of folic acid (see Figure 5.25).

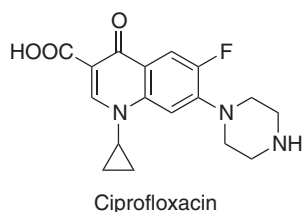


Figure 5.21 Chemical structure of quinolone ciprofloxacin.

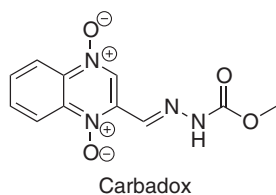


Figure 5.22 Chemical structure of quinoxaline carbadox.

Figure 5.23 Chemical structure of streptogramin pristinamycin IA.

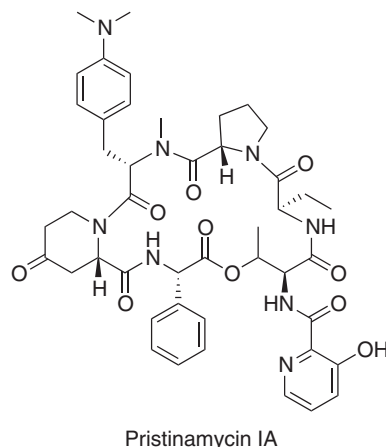


Figure 5.24 Chemical structure of sulfanilamide.

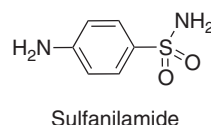
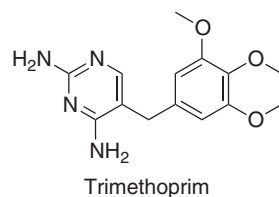


Figure 5.25 Chemical structure of trimethoprim.



Others ABs: Another type of antibiotics have been used in the treatment and prevention of bacterial infections such as aureolic acid (plicamycin), amino acid derivatives, aziridines, benzenoids, benzimidazoles, coumarin-glycosides, diphenyl ether derivatives, epipolythiodioxopiperazines, fatty acid derivatives, glucosamines, indol derivatives, macrolactams, nucleosides, peptidyl nucleosides, phenicoles, pyridines, and pyrimidines, statins, steroids, and taxoides.

Some of the different classes of ABs, such as β -lactams (amoxicillin and penicillin), are the most widely used ABs for human therapy, while other ABs are used for livestock for therapeutic, prophylactic, and sub-therapeutic purposes [7]. In veterinary medicine, ABs are used to treat disease or to increase feed efficiency and improve growth rates [8]. The major classes of ABs used for livestock are tetracycline, sulfonamides, aminoglycosides, β -lactams, macrolides, lincosomides, and ionophoric monensin.³ For example, monensin, approved by the USFDA is routinely used in the dairy industry mostly for sub-therapeutic purposes for improving feed efficiency and weight gain [9]. Similarly, the macrolide tylosin is also used for weight gain and to improve feed efficiency.

ABs could be also designated as being extremely toxic to microorganisms (EC_{50} below 0.1 mg L^{-1}) and very toxic to algae (EC_{50} between 0.1 and 1 mg L^{-1}) [10].

³ Trade name rumensin.

5.2.2 The Problem of the Resistance of Antibiotics

ABs come within a therapeutic class where human-health preservation and environmental disturbance are closely related. The major concern is to prevent the development of resistance mechanisms of bacteria, which can subsequently compromise public health [11]. Even considering the use of these products at sub-therapeutic concentrations, studies suggest the development of bacterial resistance and further potential cross-resistance between different classes of AB used by humans [10]. In addition, about 50% of the 100 million ABs doses prescribed each year in the United States for humans are either unnecessary or are wrong medications [12, p. 161]. Table 5.3 shows the emergence of more prescribed ABs over the last few decades, indicating when resistance was observed.

Animals often do not completely metabolize ABs and therefore excrete part of the unmetabolized ABs through feces and urine. It has also been reported that once the ABs are administered, nearly 90% is excreted into the environment in partially metabolized form [15].

5.2.3 Antibiotics in the Environment

Once ABs are released into the environment, some are relatively stable and do not degrade under biotic or abiotic degradation conditions. Occurrence of ABs in the environment is a cause of concern due to potential human-health and ecological consequences, particularly, antimicrobial resistance.

ABs or their transformation products have diverse origin: hospitals, domestic wastewaters, pharmaceutical manufacturing facilities, or fish farms. Resistance can result in the case of exposure of living bacteria to residual ABs in waters, and experimental evidences suggest that AB-resistant bacteria are more prevalent

Table 5.3 Evolution of resistance to antibiotics.^{a)}

Antibiotics	Year deployed	Resistance observed
Sulfonamides	1930s	1940s
Penicillin	1943	1946
Streptomycin	1943	1959
Chloramphenicol	1947	1959
Tetracycline	1948	1953
Erythromycin	1952	1988
Vancomycin	1956	1988
Methicillin	1960	1961
Ampicillin	1961	1973
Cephalosporins	1960s	Late 1960s
Linezolid	2000	2003
Daptomycin	2003	2005

a) Data taken from Refs. [13, 14].

downstream of urban STP discharges [16]. The appearance of ABs in wastewater from hospitals deserves special mention because this has a higher concentration of these products than does conventional urban wastewater [17].

Global antibiotic consumption grew by 30% during 2000–2010 [18]. It has been estimated that between 2010 and 2030, the use of ABs in animal-feed production will increase by 67%, from approximately 63,000 to 106,000 t [19], and consequently, the possibility of water contamination with such compounds will increase. Human and veterinary ABs have been detected in different matrices. These pollutants are continually discharged into the natural environment as either parent compounds or metabolites/degradation products or both forms by a diversity of input sources.

ABs that are used in livestock production are excreted through the urine and feces of animals and often appear in manure. This can cause some problems in terrestrial ecosystems such as adverse effects on nitrifying bacteria [20] or growth inhibition of crop plants and weeds by bioaccumulation [21].

Another major environmental risk involves the massive use of ABs in livestock and fish farms for preventing or treating microbial infections to improve production. Residual amounts of ABs result from waste and some amounts of ABs are incorporated into the human diet through food. The WHO recommended that the antimicrobial agents used in animal feed for growth promotion should be avoided when containing products of the same classes used by humans. By now, risk-based evaluation has demonstrated their safety.⁴ At least 17 classes of ABs, have been approved for growth promotion and feed efficiency, such as tetracyclines, penicillins, macrolides, lincomycin (analog of clindamycin), and virginiamycin (analog of quinupristin/dalfopristin) [22].

When dispersed in the fields as fertilizer, manure can contaminate the soil and, consequently, surface and groundwater through runoff or leaching [23–25]. Similarly, ABs consumed by humans are introduced into the environment through excretion (urine and feces), entering the sewer network and reaching the WWTPs (see Figure 4.2 in p. 60).

The presence of various ABs in surface water, sediments, municipal wastewater, animal waste lagoons, and groundwater underlying lagoons was confirmed by several studies [26–28]. Some studies have revealed that more than 30 AB types can be found in influents and effluents of sewage as well as in surface, ground, and drinking waters [24].

The presence of ABs in environmental matrices has been investigated [8], and in 1982, the first case of water contamination (surface water) was reported, when Watts *et al.* [29] detected macrolides, tetracyclines, and sulfonamides in English rivers at concentrations of 1 mg L⁻¹.

After this case, several studies on AB residues in aquatic ecosystems have reported the contamination of surface waters [11, 30–38] groundwaters [34, 39, 40], sea waters [34, 41], drinking water [38, 42], WWTP effluents [38, 41, 43, 44], and hospital wastewaters [30, 31, 38, 40, 44–46]. ABs have also been detected in terrestrial matrices and biosolids [30, 33, 37, 47–50]. Anhydro

⁴ WHO global principles for the containment of antimicrobial resistance in animals intended for food. Report of a WHO Consultation, Geneva.

erythromycin is among the most frequently detected drug in groundwater [51, 52].

Kümmerer [53, 54] has carried out an extensive study on the uses, sources, occurrence, and degradation of the most common ABs in the aquatic environment. Although many of the data provided are based on local samples, many of the conclusions drawn may be extended to a global scope. The key idea is that at present, there is insufficient information available to draw conclusive evidence on the significance and impact of the presence of resistant bacteria that have risen in the environment because of the presence of residual ABs in waters, hampering the assessment of the potential risks related, for instance, to human health and ecosystem functions.

A review focusing on the analytical methodologies for determining these kinds of compounds in aqueous matrices [55] has been published.

5.2.4 Degradation/Removal of Antibiotics

To prevent environmental matrices contamination, several processes to degrade/remove ABs have been studied. Review articles have appeared on the oxidation technologies for the removal of several PCs [56–59], as well as provided a general review of ABs in the aquatic environment, which covers possible disposal methodologies [53].

The need to reduce the environmental risk resulting from the occurrence of these substances requires the development of feasible methods for their elimination [60]. Many drugs are resistant to chemical degradation and biodegradation. Their elimination during the processes of wastewater treatment and water self-purification occurs only to a minor extent, or not at all, due to their high persistence [61]. In such cases, advanced oxidation processes are efficient novel methods for water treatment, which have afforded very good results. Radicals generated during advanced oxidation processes can lead to the remediation of an extensive variety of organic pollutants [62].

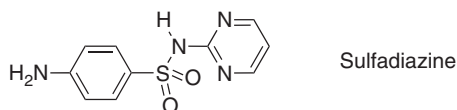
Advanced oxidation technologies are characterized by the production of the highly oxidative hydroxyl radical at ambient temperatures for oxidative destruction of organic compounds, which can ultimately lead to complete mineralization with the formation of CO_2 , H_2O , and mineral acids [62].

5.2.5 An Example of ABs in the Environment: Sulfonamides

The first antimicrobial agents to be used were sulfonamide drugs, which represented the AB revolution in medicine. However, due to their high toxicity, sulfonamides are now being replaced by other chemotherapeutics. Nevertheless, antimicrobial agents from the sulfonamide group are still currently used in animal husbandry for veterinary purposes or as growth promoters (particularly in large-scale animal farming and intensive livestock treatment) [1].

Sulfadiazine is a sulfonamide widely used as a veterinary AB to prevent and treat diarrhea and other infectious diseases (see Figure 5.26). It is resistant to chemical degradation and biodegradation. The main route of entry of these compounds to groundwater is the extensive use of manure from medicated animals

Figure 5.26 Chemical structure of Sulfadiazine.



in crop fields [63]. This substance infiltrates the soil with manure during the fertilization of agricultural land [64].

Sulfadiazine was detected in seawater at a concentration of $2.5 \mu\text{g dm}^{-3}$, and different drugs from sulfonamide group occurred over a wide range: $3\text{--}41 \mu\text{g dm}^{-3}$ in sewage sludge, $0.48\text{--}2.64 \mu\text{g dm}^{-3}$ in cow's milk, and $16\text{--}39 \mu\text{g dm}^{-3}$ in poultry and pork meat.

The presence of sulfonamide AB TPs in groundwater was more noticeable in agricultural areas than in urban groundwater [65]. Acetylated metabolites of sulfonamide ABs were frequently detected in groundwater below agricultural land in Catalonia (Spain). In all cases, their concentrations were below 57 ng L^{-1} [65]. Conversely, the sulfamide metabolites, desamino-sulfamethoxazole and 4-*N*-sulfamethoxazole, were barely detected in groundwater, with maximum levels of 6 and 4 ng L^{-1} , respectively [66].

5.3 Estrogens and Hormonal Compounds

Hormonal compounds are one of the most noteworthy classes of PCs because of their common use and serious impacts on humans and animals [67]. The most notable natural estrogens includes E1, E2, and E3, which are mainly excreted by humans (see Figure 5.27). A notable synthetic estrogen such as EE2, which is used by women for contraception, causes detrimental effects on the environment such as feminization of male fish, alternation of DNA integrity, immune cell number, and ability to break down pollutants [27].

E2 is one of the natural estrogen hormones circulating in the human body and is indeed common to all vertebrates [68]. It is also provided as an active ingredient in many hormone-replacement therapies and as an ester pro drug (estradiol valerate) in some new contraceptive formulations. The most remarkable contributors of the natural E2 load in the United Kingdom are pregnant and menstrual women providing an estimated 63% and 18%, respectively [69].

Estrogens together with other classes of compounds such as pesticides, PAHs, phthalate plasticizers, certain PCBs, dioxins, furans, and alkylphenols are EDCs [70]. Thus, they may interfere with the endocrine and reproductive activities of animals (see Section 5.4). The presence of estrogens in waters implies a risk for the health of wildlife [71].

5.3.1 Estrogens in the Environment

The main source of estrogens in the environment is domestic wastewater. Between 10 and $100 \mu\text{g}$ of E1, E2, E3, and EE2 are excreted daily by women through their menstrual cycle [72]. The excretion of estrogens in pregnant women can reach the 30 mg d^{-1} concentration. Estrogens are excreted in human

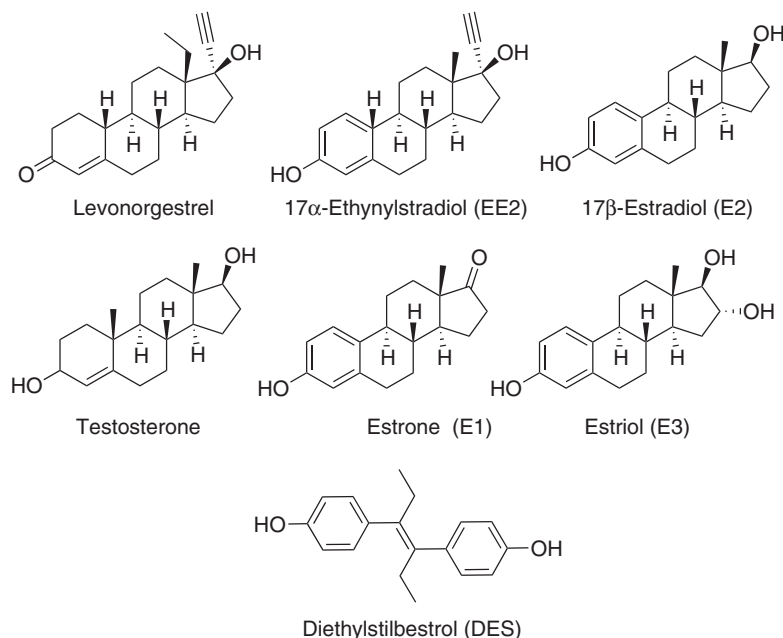


Figure 5.27 Chemical structure of some steroids and hormones.

urine as conjugates of sulfuric acid and glucuronic acids [70]. However, estrogens can also be derived from animal manure [73].

Given the amount of E2 excreted by women in hormone-replacement therapies and the proportion present as the parent or glucuronide, only 3–10% of the pharmaceutical E2 ingested would be excreted [74]. This implies that for the countries with available data (see Table 5.4), only 1–8% of the total E2, arriving at a STP would have originated from pharmaceutical sources.

Miege *et al.* [80] described a detailed analytical method for E1, E2, 17α-estradiol (α-E2), E3 and EE2 estrogens. The probable excretion rate of EE2 by humans has been extensively reviewed. The values for EE2 consumption in different European countries showed only a small variation in individual EE2 consumption values (from 0.84 in Sweden to 2.59 $\mu\text{g cap}^{-1} \text{d}^{-1}$ in the Netherlands) [69].

Natural and synthetic hormones are present at measurable levels in effluent wastewaters and in surface waters [81], and therefore, they are likely to reach aquifers. During soil passage, these compounds can be adsorbed onto soil particles due to their low aqueous solubility (1.7–57.8 mg L^{-1}) and moderate hydrophobicity ($\log K_{\text{ow}}$ 2.5–4.0),⁵ and they could also biodegrade [82]. Consequently, hormone concentrations in groundwater are usually in the low ng L^{-1} range. These low concentrations should not be overlooked because estrogenic effects have been noted at concentrations of E2 and EE2 as low as 1 ng L^{-1} [83].

EE2 is still considered the most persistent of the steroid estrogens, with a modest half-life in water of 17 days and also a slow photodegradation rate [84].

⁵ Physical properties database. Fate Pointers Search Module of the Syracuse Research Company (SRC, Inc.); 2014 <http://esc.syrres.com/fatepointer>.

Table 5.4 Maximum concentrations (ng L⁻¹) of hormones in different types of water in various locations.^{a)}

Compound	WWTP/ STP effluents			Freshwater (rivers, canals)			Groundwater	
	United States ^{b)}	Sweden ^{c)}	S. Korea ^{d)}	Austria ^{e)}	France ^{f)}	S. Korea ^{d)}	France ^{f)}	Austria ^{e)}
E1	n.d.	70	36	4.6	0.3	5.0	3.5	1.6
E2	n.d.	9.2	<1.0	1.2		n.d.		0.79
α -E2	180			0.31	n.d.		1.6	0.21
EE2		n.d.	1.3	0.33	n.d.	n.d.	3	0.94
E3	590		25	1.9		n.d.		0.16
Testosterone			1.1		3.4	n.d.	6	
Androstenedione			3.5		1.8	2.6	2.6	

a) n.d. = not detected.

b) Data taken from Ref. [75].

c) Data taken from Ref. [76].

d) Data taken from Ref. [77].

e) Data taken from Ref. [78].

f) Data taken from Ref. [79].

E1 was detected only in 0.6% of the samples and at a maximum concentration of 4 ng L⁻¹ in a pan-European groundwater survey [85]. In a study conducted in the Rhône-Alpes region in France, mean concentrations in groundwater were below 1 ng L⁻¹; that is, E1, α -E2, E2, and 4-androstenedione yielded 0.7, 0.7, 0.4, and 0.8 ng L⁻¹, respectively [86].

The most ubiquitous hormones in the samples investigated were testosterone, 4-androstenedione, and progesterone, whereas the most abundant compound was levonorgestrel, with concentrations of up to 4 ng L⁻¹ [86]. Slightly higher concentrations of E2 (0.7 ng L⁻¹) were measured in groundwater used as a drinking water source in the Yangtze river (China). However, groundwater samples containing this compound did not show ER agonist activity [87]. Low estrogen concentrations (<1.7 ng L⁻¹) built up in groundwater in Arizona [88].

Conjugated estrogens have rarely been detected in groundwater because, despite their high water solubility, they are likely to hydrolyze in the environment [89]. For instance, estradiol-3-glucuronide was measured at an average concentration of 425 ng L⁻¹ in a well located on agricultural land where swine manure was applied [89]. Estrone-3-sulfate was also determined at a maximum concentration of 4 ng L⁻¹ in groundwater affected by a residential septic system [90].

Miege *et al.* [91] reported that hormones, including estrogens, were the most commonly studied molecules in sewage water (30% of the reviewed data) in France. The concentrations of E1 were between 22 and 181 ng L⁻¹. E2 was quantified at being between 3.5 and 50 ng L⁻¹ while α -E2 registered between 0.8 and 10.3 ng L⁻¹. In this work, EE2 was not detected in any influent samples, but was found in other studies [92].

Among the 12 estrogens reported on the occurrence in Italian waters, the most frequently investigated has been the synthetic estrogen EE2, and the female hormones, E1 and E3. Maximum concentrations of estrogens in surface water of Italy were not high ($\leq 50 \text{ ng L}^{-1}$). The highest maximum concentrations ($>10 \text{ ng L}^{-1}$) were reported for E2 (50 ng L^{-1}) and E1 (47 ng L^{-1}) in the Lambro river [93] and for E2 (12.9 ng L^{-1}) in surface water of Liguria [94]. Table 5.4 shows some examples of the occurrence and concentration of hormones in effluents, freshwater, and groundwater in different countries.

High concentrations of E1 ($40\text{--}390 \text{ ng L}^{-1}$) and testosterone (30 ng L^{-1}) were determined in shallow groundwater affected by lagoons containing wastewaters from concentrated animal-feeding operations [95]. Hormone levels in the $\mu\text{g L}^{-1}$ range, which were much higher than those usually measured in wastewater effluents, were present in leachate from cattle-carcass burial sites. Concentrations of E2, E1, and testosterone in this type of leachate were in the ranges of 32–20,069, 77–2,706, and 13–235 ng L^{-1} , respectively [63]. Thus, high concentrations of these compounds in underlying groundwater could be expected.

Land irrigation with reclaimed water, concentrated animal-feeding operations, and cattle-carcass burial are activities that may increase hormone concentrations in groundwater [63]. While hormone levels are usually in the low ng L^{-1} range in groundwater, they increase sharply in aquifers impacted by these practices. For instance, up to 1745 ng L^{-1} of E3 were detected in the groundwater of an area irrigated with reclaimed water. Despite the fact that E3 was the most ubiquitous compound, EE2, E1, and E2 were also present, with maximum concentrations of 230, 79, and 147 ng L^{-1} , respectively [96].

5.4 Drugs with Endocrine Disruption Properties

The endocrine system is composed of glands and organs that secrete hormones into the bloodstream. Hormones travel with the blood to different parts of the body to prompt specific responses. It is a complex system that controls important body functions such as growth, metabolism, and reproduction. Endocrine disruptors are chemicals that may interfere with the body's endocrine system and provoke harmful developmental, reproductive, neurological, and immune effects in both humans and wildlife.

The WHO defines an EDC as:

An exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny.

The EPA defines environmental EDCs as exogenous agents that interfere with the:

Synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development, and/or behavior.

The USEPA tried to establish the endocrine disruptor screening program (EDSP) to develop official screening methods and toxicity testing strategies for approximately 87,000 compounds. The European Organization for Economic Co-operation and Development (OECD) also has made an effort to develop a reliable method to confirm the significance of EDCs [97]. EDCs are known as belonging to a class of chemicals that have xenobiotic and exogenous origins while mimicking or inhibiting the natural action of the endocrine system, such as synthesis, secretion, transport, and binding in animals and humans. They maintain the homeostasis, reproduction, metabolism, development, and/or behavior of living species. The primary effects of EDCs, as described earlier, are either the mimicking or inhibition of the behavior of natural hormones, such as estrogen, testosterone and/or thyroid. Depending on the endocrine end points, they can be defined as estrogenic, androgenic, or thyroidal compounds [98].

Evidence that several natural and synthetic compounds can cause endocrine disruption has existed since as early as 1930. The issue gained public awareness in the 1950s and 1960s, with the discovery that DDT, a widely used pesticide, had endocrine-disrupting properties. In the 1980s and 1990s, evidence began to accumulate that a diverse range of chemicals can disrupt the endocrine system of some species, even at very low concentrations in the order of parts per trillion (ng L^{-1}).

Examples of many chemicals (potentially endocrine disruptors) are the following:

Veterinary and human antibiotics: Trimethoprim, erythromycin.

Analgesics and anti-inflammatory drugs: Codein, ibuprofen, paracetamol, acetylsalicylic acid, diclofenac, fenoprofen.

Psychiatric drugs: Diazepam.

Lipid regulators: Bezafibrate, clofibric acid, fenofibric acid.

Lipid regulators: Metoprolol, propranolol, timolol, betaxolol, sotalol, atenolol, metoprolol.

β -Blockers: Metoprolol, propranolol, timolol, betaxolol, sotalol, atenolol, metoprolol.

β_2 -Sympathomimetics: Terbutalin, salbutamol.

X-ray contrast media: Iopromide, iopamidol, diatrizoate.

Steroids and hormones: Estradiol, estrone, estriol, diethylstilbestrol.

Fragrances: Nitro, polycyclic, and macrocyclic musks.

Sunscreen agent: Benzophenone, methylbenzylidene camphor.

Insect repellents: *N,N*-Dimethyltoluamide (DEET).

Antiseptics: Triclosan, chlorophene.

Flame retardants: Polybrominated diphenyl ethers (PBDEs), tetrabromobisphenol A, tris(2-chloroethyl)phosphate (TCEP).

Surfactants and surfactant metabolites: Alkylphenol ethoxylates (APEO), alkylphenols, alkylphenol carboxylates, pentafluorooctane sulfonate (PFOS).

Industrial additives and agents: Chelating agents (EDTA), aromatic sulfonates.

Gasoline additives: Dialkyl ethers, methyl 4-butyl ether (MTBE).

Disinfection by-products: Iodo-THMs, bromoacids, bromoacetonitriles, bromoaldehydes, cyanoformaldehyde, bromate, NDMA.

Algal and cyanobacterial toxins: Saxitoxin, anatoxin-a, microcystin, nodularin, cylindrospermopsin.

The particular characteristics of EDCs, such as their occurrence at trace concentration levels and with extremely diverse groups, make the detection and analysis procedures quite challenging. To overcome difficulties in the analysis, various methods have been developed. Currently, the most predominating methodological approach designed to analyze EDCs incorporates a MS-based analysis process.

The adverse effects of EDCs on the reproductive health in humans and wildlife have become an issue of major concern among the public [99]. The correlation between exposure to EDCs and the health of human and wildlife, including any unknown long-term impacts, is an extremely complex and controversial issue which is difficult to confirm.

The detection limits of several analytical methods are summarized in Table 5.5 [39, 100, 101]. The detectable presence of many EDCs in various water environments, including wastewater, surface water, sediments, groundwater, and drinking water has been reported [83, 102–104].

Various adverse health effects of EDCs have been reported [77, 106]–[108]. The first issue of EDCs reported was related to the incomplete removal of steroids in the wastewater-treatment process [109]. In the 1980s, the presence of several human hormones and PCs were first reported in the treatment of wastewater and discharged aquatic environments [110, 111]. Currently, many types of EDCs were detected in a wide range of natural and engineered environments across the world, including surface water, groundwater supplies, wastewater effluents, seawater, and sediment [77, 78, 83, 112, 113].

The main concern about drugs with endocrine-disruption properties are molecules with hormonal activity as “natural hormones” or “synthetic,” such as EE2. Figure 5.28 shows examples of two common classes of potential endocrine

Table 5.5 Reported detection limit of different analytical methods for various EDCs in water samples.^{a)}

Method [References]	Detection limit (ng L ⁻¹)	Method [References]	Detection limit (ng L ⁻¹)
E-Screen [101]	0.27	SPE–GC/MS [100]	12–32
ER-CALUX ^{b)} [101]	0.14	GC–MS/MS [101]	0.05–2.4
YES ^{c)} [101]	0.3–30	SPME–HPLC [101]	0.064–1.2
ELISA ^{d)} [101]	20–40	SPE–HPLC/ESI-MS/MS [39]	3.5–44
LC–MS/MS [100]	0.08–33		

a) Data taken from Ref. [105].

b) Estrogen responsive chemically activated luciferase expression.

c) Yeast estrogen screen.

d) Enzyme-linked immunosorbent assay.

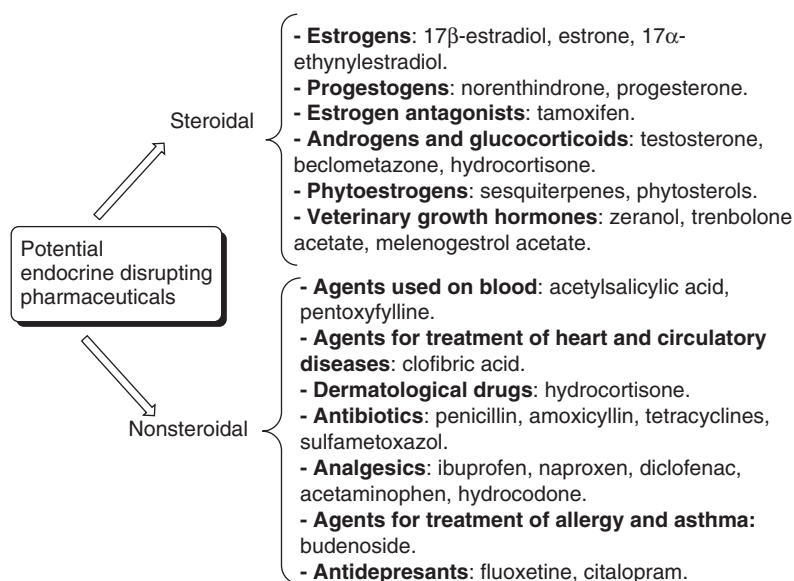


Figure 5.28 Scheme of the potential endocrine disrupting PCs [114].

disrupting PCs, that is, steroidal and nonsteroidal. Steroids that are used as estrogens are suspected to be a cause of feminization in male fish. This phenomenon has been observed worldwide. As examples of these studies, Puy-Azurmend *et al.* [115] described, even in a specially protected areas, deleterious effects on fish development and reproduction already noticed for instance in English rivers [116]. These chemicals can be detected too in many areas downstream of a STPs [70].

Following a series of surprising observations on the effects of fish being exposed to sewage effluent in the mid 1980s in the United Kingdom, a series of methodical studies revealed that something in the effluent could provoke endocrine disruption [117]. Field surveys then revealed that endocrine disruption of fish was widespread in wild fish caught in proximity to STPs [116] and that the most potent component of that effluent was the fraction containing steroid estrogens [118]. Among those steroid estrogens, E2 and the synthetic estrogen EE2 were demonstrated to be the strongest [119]. These observations were repeated by scientists throughout the world. While the disrupting effects of E2 and EE2 at low ng L⁻¹ exposure concentrations on individual fish are undeniable, the assessment of the effect of that disruption on fish populations is less sure [120].

Whole organism assays use the endocrine-disruption process in amphibians, fish, birds, and insects in order to monitor the EDCs in aquatic environments. The responses in the organisms are manifested as deformities, reproductive deficiencies, bad egg and offspring development, and defective serum protein production, such as vitellogenin.

The real effects associated with the presence of low levels of PCs may be difficult to evaluate over the long term. Low levels of PCs with estrogenic properties

detected in waters used for human consumption may not alter naturally occurring internal levels associated with natural physiological fluctuations, which can vary in humans with age, sex, or reproductive status [121].

Conventional separation techniques, such as coagulation, flocculation, and precipitation, are not effective in removing EDCs, especially for low-molecular-weight compounds [122]. In addition, conventional biological processes, such as activated sludge, biofiltration, and soil-aquifer treatment, have shown limited EDCs removals [92, 123]. Advanced separation processes, such as adsorption, membrane filtration, and ion exchange, normally show superior removal efficiencies (up to 95%), depending on the compounds tested [124].

5.5 Analgesic, Anti-inflammatory, Antiarthritic, and Antirheumatic Compounds

A significant portion of pharmaceutical pollution in wastewater is composed of anti-inflammatory and analgesic drugs, which are used as inflammation reducers and pain relievers, respectively [125]. Both groups of chemicals are extensively used without a prescription with an estimated annual consumption of several hundred tons in developed countries [126].

The most common classes of these types of drugs are the following [127, 128]:

Analgesics Opiates and opioids, morphines, pethidine, pentazocine, dextro-propoxyphene, acetylsalicylic acid and derivatives, and paracetamol.

Anti-inflammatories Pirazolones, phenylbutazone, acetic acid derivatives, indometacin, sulindac, diclofenac, oxicams, piroxicam, propionic acid derivatives, ibuprofen, naproxen, ketoprofen, fenoprofen, fenemates, mefenamic acid, and tolafenamic acid.

Analgesics are pain-relief drugs that include narcotic and non-narcotic analgesics, as well as NSAIDs. They act in various ways on the nervous systems and are widely used to alleviate the pain present in almost all diseases [129].

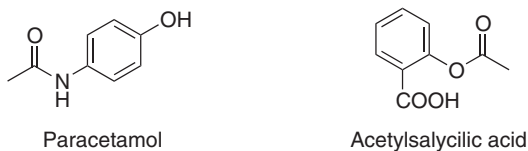
Common non-narcotic analgesics include acetaminophen and acetylsalicylic acid. Narcotic analgesics include codeine, methadone, morphine, and oxycodone. NSAIDs include diclofenac, fenoprofen, ketoprofen, mefenamic acid, indometacin, naproxen, and ibuprofen [130].

Although excretion is the major source of water and soil pollution by PCs, other sources such as emission from production sites, accidental manufacture spills, direct disposal of surplus drugs in households, underground leakage from sewage infrastructures, therapeutic treatment of livestock in fields, and effluents from farms are of significance, as well [131, 132].

5.5.1 Non-Narcotic Analgesics Drugs

Common non-narcotic analgesics include the highly prescribed paracetamol and acetylsalicylic acid (see Figure 5.29).

Figure 5.29 Chemical structure of paracetamol and acetylsalicylic acid.



Paracetamol (acetaminophen) is a mild analgesic that is commonly used in combinatory drugs for the relief of fever, headaches, and some minor pains [56]. Acetaminophen is a weak inhibitor of the cyclooxygenase enzyme, whose side effects are associated mainly with the formation of hepatotoxic metabolites. It is metabolized in the liver to sulfate and glucuronide conjugates and excreted in the urine [133]. Hence, the source of paracetamol pollution in surface water is primarily sewage-plant effluents [134].

Acetylsalicylic acid is one of the most popular painkillers that is readily degraded to the more active salicylic acid and two other metabolites (*o*-hydroxyhipuric acid and gentisic acid), all of which are easily eliminated in conventional sewage-treatment operations [135].

5.5.2 Narcotic Analgesics Drugs

Narcotic analgesics include the opiates: codeine, methadone, morphine, and oxycodone (see Figure 6.1 in p. 172). Morphine has strong activity, and its presence as complex mixtures in surface waters – together with residues of many therapeutic drugs – may lead to unforeseeable pharmacological interactions, with toxic effects on aquatic organisms [136].

5.5.3 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs are weak acids acting by reversible or irreversible inhibition of one or both isoforms of the cyclooxygenase enzymes (COX-1 and COX-2) involved in the synthesis of different prostaglandins from arachidonic acid [137]. Prostaglandins also play a key role in the synthesis of bird eggshells and, on inhibiting its synthesis, shell thinning has been observed [138]. Diclofenac, mefenamic acid, indometacin, ketoprofen, naproxen, fenoprofen, ibuprofen, and tolmetin are well-known representatives of NSAIDs (see Figure 5.30).

Due to the widespread use of NSAIDs, this group of drugs is often detected and determined in surface waters, in influent and effluent wastewaters, and in drinking waters (see Figure 5.6). NSAIDs residues have been analyzed by LLE using the LC–MS/MS method. Although the concentrations of these compounds in surface water are relatively low (from ng L^{-1} to mg L^{-1}), continuous release and chronic exposure to these substances can result in adverse effects on aquatic life and is of potential risk to human health [139].

World-wide investigations on the contamination levels of anti-inflammatory drugs have shown that individual concentrations are within the $\mu\text{g L}^{-1}$ range in aquatic and surface waters, signifying the high proportion of municipal sewage effluents [132, 140]–[144]. These drugs have been detected in STP influents

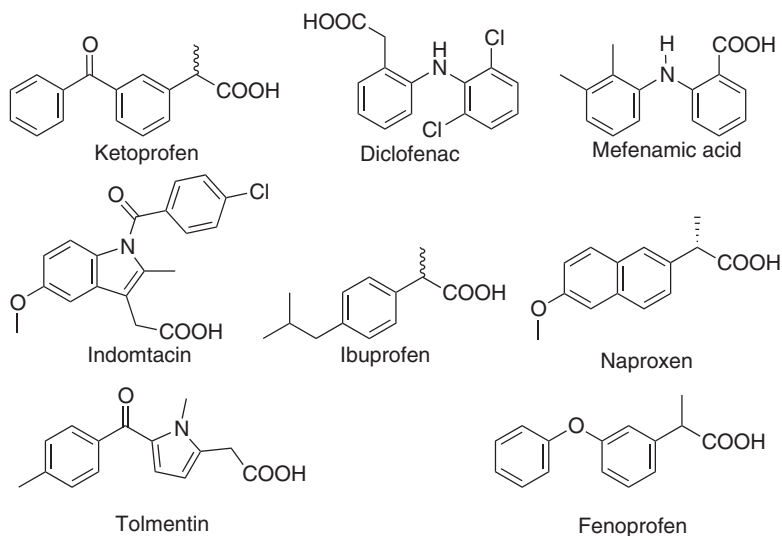


Figure 5.30 Chemical structure of most common NSAIDs.

and effluents and in surface-water samples in Switzerland [39, 140, 145–147]. The results obtained also show the presence of ibuprofen, naproxen, ketoprofen, and fenoprofen at ng L^{-1} levels in river water.

5.5.3.1 Diclofenac

Diclofenac is a highly consumed anti-inflammatory and very commonly used in human medical care as an analgesic, antiarthritic and antirheumatic compound (see Figure 5.30) [148]. It is used worldwide and has a production volume estimated to be in hundreds of tons annually [148]. About 940 t yr^{-1} of diclofenac is estimated to be consumed globally [149]. This compound is readily metabolized to hydroxylated (4'-hydroxy-DCF; 4',5-dihydroxy-DCF; 3'-hydroxy-DCF; 5'-hydroxy-DCF) or methoxylated derivatives (3'-hydroxy-4'-methoxy DCF) and further conjugated to glucuronides [150]. As acid, diclofenac occurs in the aquatic environment as an anion, which explains its high solubility and very low volatilization.

As one of the most widely used drugs, diclofenac was one of the first PCs to be detected in the aquatic environment [151]. Once it reaches the aquatic environment, many reactions, transformation, or translocation processes occur, reducing its concentration in the water of rivers [152] and lakes [151]. Biodegradation, bioaccumulation, biomagnification, chemical degradation, photodegradation, adsorption to particles and sedimentation, infiltration in sediment and sorption, precipitation, or volatilization are some possibilities. Due to their constant load, pharmaceuticals are considered “pseudo-persistent” as there is a permanent background concentration. Derivatized diclofenac can be analyzed by GC/MS [153]. However, some studies [154, 155] used HPLC instead to measure diclofenac, with the advantage that no derivatization is needed prior to measurement, as compared to GC/MS [156]. Recent values for diclofenac

consumption in different European countries showed consumption values from 449 to 2613 $\mu\text{g cap}^{-1} \text{d}^{-1}$ in France [69].

Despite research on the occurrence and fate of diclofenac in aquatic environments [152, 157], further questions on different aspects, for example, photo-degradation [158], behavior in sediment infiltration [154], and ecotoxicological assessments [155] have been investigated, thus making diclofenac one of the few well-investigated PCs today.

Characteristically, diclofenac has a poor removal efficiency in conventional sewage treatment [149], and has been detected in WWTP effluents in Germany [150], Spain [159], and Canada [160]. This drug has been detected in STP effluents at maximum concentrations of 2.4 g L^{-1} [161] and 1.42 g L^{-1} [162] in Switzerland and Belgium, respectively. The drug has been detected in river water [163], well water at concentrations of about 2 ng L^{-1} [164], and in groundwater at a maximal concentration of 380 ng L^{-1} [165, 166]. Diclofenac has also been found in river water [167], groundwater [168], hospital effluents [169] and drinking water but at concentrations in the order of ng L^{-1} . Biosolids contained diclofenac at concentrations of up to 381 $\text{ng g}^{-1} \text{dw}$ [170].

Among the NSAIDs, diclofenac has shown to have acute toxic nature with effects being observed at concentrations below 100 mg L^{-1} [125, 155]. It has also inhibited the growth of marine phytoplankton *Dunaliella tertiolecta* for concentrations of 25 mg L^{-1} and above [171]. Diclofenac is acutely toxic to birds [172] and alters the composition of exposed river biofilm communities [173]. Schmitt-Jansen *et al.* [155] assessed the phytotoxicity of diclofenac and its transformation products. Furthermore, diclofenac has been reported as the causal agent of outbreaks in the poisoning and population decline of three species of vulture in Asia [174]. This example might will be the worst ever case of wildlife poisoning by a chemical [175].

Studies have suggested that low $\mu\text{g L}^{-1}$ concentrations of diclofenac adversely affect fish [138], raising concern that diclofenac might pose a threat to wild fish. However, a recent study has failed to support the results of these earlier studies, and instead found that adverse effects on fish occurred only when the environmental concentration approached 1 mg L^{-1} [176], which is far higher than any river concentration is likely to be.

5.5.3.2 Ibuprofen

Ibuprofen is commercially available as 2-(4-isobutylphenyl) propionic acid, and used widely in the treatment of rheumatic disorders, muscular pain, and fever (see Figure 5.30) [177]. It is an antipyretic drug that is recognized with a huge global consumption rate [140]. The anti-inflammatory drug ibuprofen and mefenamic acid are the substances, most sold, with 17 t yr^{-1} in Switzerland [157].

Ibuprofen is an NSAID with documented chronic toxicity. Ibuprofen is rapidly excreted in the form of various conjugates, for example, hydroxy-ibuprofen, carboxy-ibuprofen, and carboxy-hydratropic acid [177], which not only have acute toxicity, but are also suspected of endocrine disruption in humans and wildlife [140].

5.5.3.3 Naproxen

Naproxen is widely used in mild-to-moderate pain relief and in treating osteoporosis, rheumatoid arthritis, menstruation discomfort, and headaches (see Figure 5.30) [178]. The drug is additionally used in veterinary medicine in appreciable quantities. Bioassay tests have shown that chronic toxicity of naproxen is higher than its acute toxicity, and by-products of photodegradation are more toxic than the compound itself [162, 179].

5.5.3.4 Ketoprofen

Ketoprofen is a anti-inflammatory drug with analgesic and antipyretic effects and is classified under acidic drugs because of the presence of a carboxylic group in its chemical structure (see Figure 5.30) [180]. The drug is metabolized mainly in conjugation with glucuronic acid (carboxylic acid), and excreted in the urine (85%) [147].

5.5.3.5 Mefenamic Acid

Mefenamic acid is classified under “anthropogenic” PCs and PCPs (see Figure 5.30) [181]. It is a diphenylamine derivative, a pollutant class with substantial environmental relevance [182]. More than 50% of an ordinary dose of mefenamic acid is recovered in the urine mainly as conjugated metabolites [147].

5.6 Psychotropic Drugs

A psychoactive drug or psychotropic substance is a chemical compound that acts primarily on the central nervous system where it alters brain function, resulting in temporary changes in perception, mood, consciousness, and behavior. The most prescribed psychotropic drugs are anticonvulsants, anxiolytics, sedatives, hypnotics, and antidepressants. These form a large share of drugs with pharmaceutical action used in the developing world. These PCs when ingested are partially metabolized, so they can be found in variable percentages together with several metabolites and conjugates in urine and feces [183].

The most commonly prescribed psychotropic medications are:

Anti-anxiety agents: Buspirone, escitalopram, chlordiazepoxide, clorazepate, and the benzodiazepines (e.g., lorazepam, oxazepam, diazepam, alprazolam, and prazepam).

Anti-depressants: Used to treat major depressive disorders and other conditions. Tricyclics antidepressants such as amoxapine, amitriptyline, desipramine, nortriptyline, doxepin, trimipramine, imipramine, and protriptyline. Selective serotonin reuptake inhibitors (SSRIs) such as citalopram, escitalopram, paroxetine, fluoxetine, and sertraline. Monoamine oxidase inhibitors (MAOIs) such as phenelzine and tranylcypromine and others such as trazadone, venlafaxine, mirtazapine, nefazodone, and bupropion (Table 5.6).

Anti-psychotics: Used in the treatment of schizophrenia and mania. Typical: haloperidol, loxapine, thioridazine, molindone, thiothixene, fluphenazine, mesoridazine, trifluoperazine, chlorpromazine, and perphenazine. Atypical: aripiprazole, clozapine, risperidone, quetiapine, and olanzapine).

Table 5.6 Concentrations of anti-inflammatory drugs and metabolites in STP effluents as well as rivers and streams.^{a)}

Substances	STP effluents		Rivers and streams	
	LOD ^{b)}	Maximum ($\mu\text{g L}^{-1}$)	LOD ^{b)}	Maximum ($\mu\text{g L}^{-1}$)
<i>Anti-inflammatory drugs</i>				
Diclofenac	0.050	2.1	0.010	1.20
Ibuprofen	0.050	3.4	0.010	0.53
Indometacine	0.050	0.60	0.010	0.20
Naproxen	0.050	0.52	0.010	0.39
Fenoprofen	0.050	n.d.	0.010	n.d.
Ketoprofen	0.050	0.38	0.010	0.12
Phenazone	0.10	0.41	0.020	0.95
Acetaminophen	0.50	6.0	0.150	n.d.
Acetylsalicylic acid	0.10	1.5	0.020	0.34
Dimethylaminophenazone	0.10	1.0	0.030	0.34
Meclofenamic acid	0.050	n.d.	0.010	n.d.
Tolfenamic acid	0.050	n.d.	0.010	n.d.
<i>Metabolites</i>				
Salicylic acid	0.050	0.14	0.010	4.1
<i>o</i> -Hydroxyhippuric acid	0.20	n.d.	0.075	n.d.
Gentisic acid	0.20	0.59	0.075	1.2

a) Data taken from Ref. [134].

b) Limit of detection, n.d.: not detectable.

Mood stabilizers: Valporic acid. Used for treating bipolar disorder.

Anti-obsessive agents: Clomipramine, fluvoxamine, paroxetine, fluoxetine, and sertraline.

Anti-panic agents: Clonazepam, paroxetine, alprazolam, and sertraline.

Stimulants: Used in the treatment of attention-deficit hyperactivity disorder (ADHD). Amphetamine, dextroamphetamine, pemoline, and methylphenidate.

Structures of the most common psychotropic drugs are shown in Figures 5.31, 5.32, and 5.33. The group of benzodiazepines, because of their massive use, is probably the most extensively studied as potential environmental pollutants, diazepam having special relevance.

5.6.1 Environmental Impact of Psychotropic Drugs

These molecules can be detected in wastewaters, and conventional methods of wastewater treatments let through residual amounts of psychotropic drugs in treated water and sludges ($>1 \mu\text{g L}^{-1}$ to ng L^{-1} order). The occurrence of these

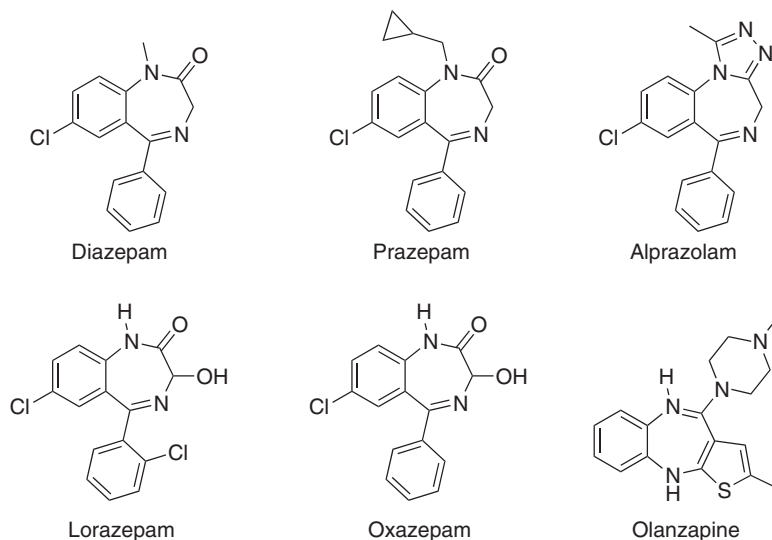


Figure 5.31 Structure of some benzodiazepine drugs.

widely used compounds in wastewaters, surface, ground, and drinking waters, soils, sediments, biosolids, and tissue has been detected in the last few years by analytical methods such as GC/MS, LC–electrospray ionization (ESI)-MS/MS or HPLC-MS/MS.

The first studies carried out on such compounds in the environment indicate their high persistence and toxicity to non-target organisms. Therefore, they are candidates to be considered as emerging pollutants and justify the growing concern about them [184].

Benzodiazepines are a group of drugs that contaminate many surface waters [134, 184–188]. Concentrations of some benzodiazepines, such as oxazepam, can reach $1.9 \mu\text{g L}^{-1}$ in treated effluent [189]. As a comparison, concentrations in effluence-dominated surface water have been reported to be as high as 0.2 and $0.6 \mu\text{g L}^{-1}$ [190, 191].

The potential risk of such compounds has been demonstrated in experiments performed on non-target organisms, Chiffre *et al.* [192] exposed larvae of Japanese medaka (*Oryzias latipes*) to six psychotropic drugs (valproate, cyamemazine, citalopram, sertraline, fluoxetine, and oxazepam) to levels above usual environmental concentrations ($0.01\text{--}10 \text{ mg L}^{-1}$), and found a change in the swimming behavior of these larvae.

Less than 10% of orally administered fluoxetine is excreted from humans either unchanged or as glucuronide [193]. Fluoxetine and sertraline have been detected in aquatic organisms residing in effluent-dominated streams [194]. The ecotoxicological effects to aquatic organisms due to fluoxetine exposure have been demonstrated [125]. It has been reported that fluoxetine increases serotonergic activity in fish, subsequently reducing aggressive behavior [195]. Perinatal exposure to fluoxetine at relevant environmental concentrations

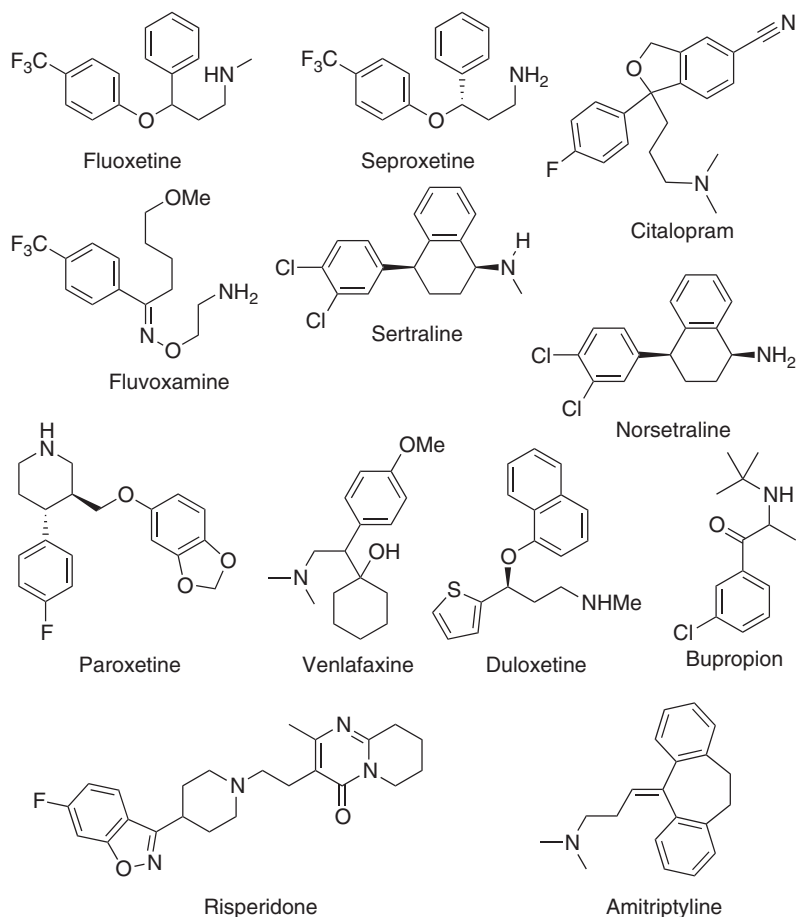


Figure 5.32 Structure of selected psychotropic drugs.

has been shown to lead to significant alterations of memory processing in one-month-old cuttlefish [196].

The most common stimulant of the central nervous system and metabolism is caffeine. It is commonly found in many drinks and some PCs with the aim of reducing physical fatigue and restoring alertness when drowsiness occurs [197]. Also, caffeine is easily found in surface waters (see Section 8.2.1) [27].

5.7 Antiepileptic Drugs

Antiepileptic drugs act on the central nervous system by reducing the overall neuronal activity. This can be achieved either by blocking voltage-dependent sodium channels (e.g., carbamazepine) or by strengthening the inhibitory effects of the γ -aminobutyric acid neurotransmitter (e.g., benzodiazepines). Carbamazepine is carcinogenic to rats but does not have mutagenic properties in mammals (see Figure 5.34) [198].

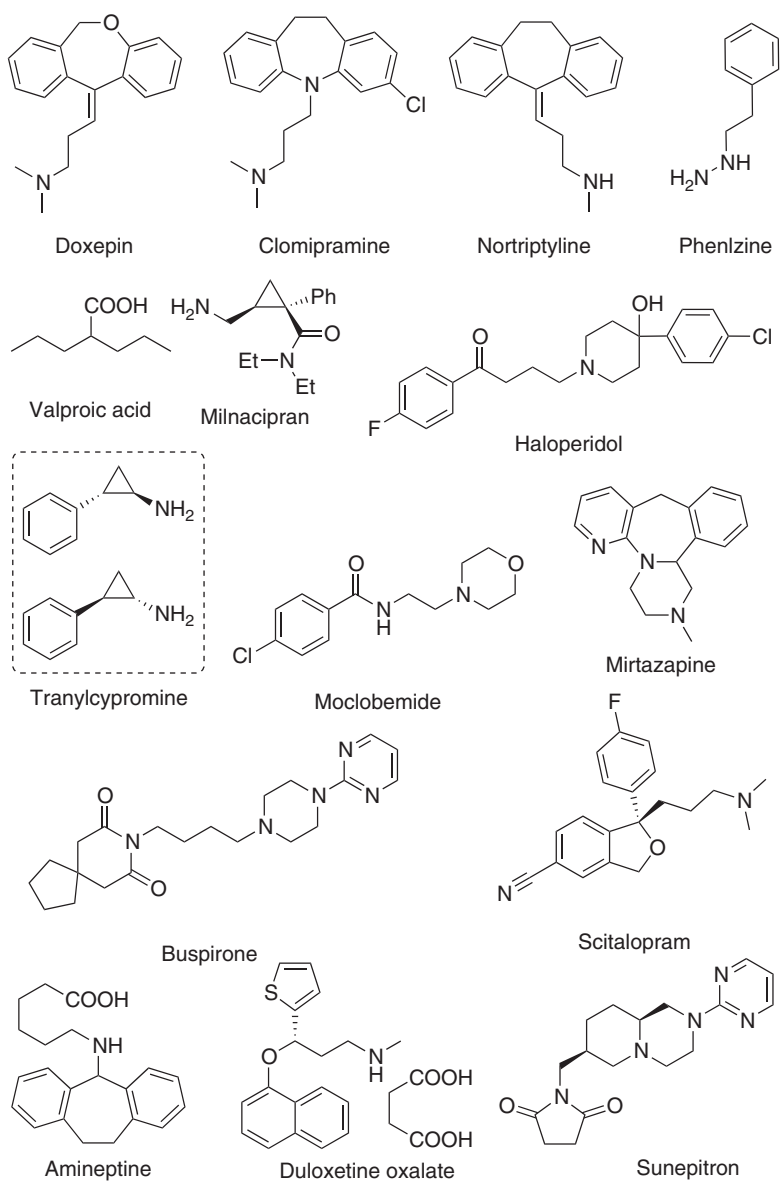


Figure 5.33 Structure of selected psychotropic drugs.

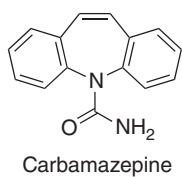


Figure 5.34 Structure of carbamazepine.

Carbamazepine, a medication used primarily to treat epilepsy and neuropathic pain, is on the WHO's List of Essential Medicines, which are the most effective and safe medicines needed in a health system.⁶

As example of the occurrence of carbamazepine, (which is excreted almost unchanged and it is resistant to environmental degradation) was detected in one study on finished drinking water in amounts of $< 1 \mu\text{g L}^{-1}$ [199]. Carbamazepine is one of the antiepileptic drugs that are most frequently detected with PCs and PCP in wastewater effluents [200], being associated with exposure to its metabolites with teratogenic effects [201].

5.8 β -Blockers/Diuretics

Anti-hypertensive are drugs used to treat high blood pressure. There are many kinds of anti-hypertensive drugs, for instance, β -blockers, calcium channel blockers, and diuretics. β -Blockers are one of the most widely prescribed classes of drugs to treat hypertension and are a mainstay treatment of congestive heart failure, angina, or abnormal heart rhythms. They act by competitive inhibition of β -adrenergic receptors, a class of receptors critical for normal functioning in the sympathetic branch of the vertebrate autonomic nervous system. Within the most commonly used β -blockers, propranolol is a non-specific antagonist, blocking both 1- and 2-receptors while metoprolol and atenolol present 1-receptor specificity [202]. Structures of some β -blockers are depicted in Figure 5.35.

These drugs have been the subject of attention in many ecotoxicity studies, because many of the receptors of such compounds could also be present in different mammals, vertebrates, and some invertebrates [203]. Fish, like other vertebrates, possess receptors in the heart, liver, and reproductive system [204]; thus, prolonged exposure to these drugs may cause deleterious effects. Because of their massive prescription, studies on the effects of β -blockers in several phytoplankton, zooplankton, and fish species are of the special concern [125].

5.8.1 β -Blockers in the Environment

An important factor regarding the occurrence of such compounds in wastewaters depends on the average of metabolized product in an organism. For example, atenolol, is excreted unchanged about 50%, metoprolol, between 10–30%, or propranolol $< 0.5\%$ [205]. Some studies have determined concentrations for these β -blockers in surface waters in the United Kingdom, at roughly 560, 215, and 12 ng L^{-1} , respectively [206].

Few studies have focused on the effects of the presence of β -blockers in aquatic environments [207]–[209]. However, as β -receptors were found in fish tissues [21], the question concerning the presence of β -blockers in waters is justified in order to anticipate the impact on these organisms. Ten β -blockers were analyzed

6 “WHO Model List of Essential Medicines (19th List)” World Health Organization. 2015. http://www.who.int/medicines/publications/essentialmedicines/EML_2015_FINAL_amended_NOV2015.pdf.

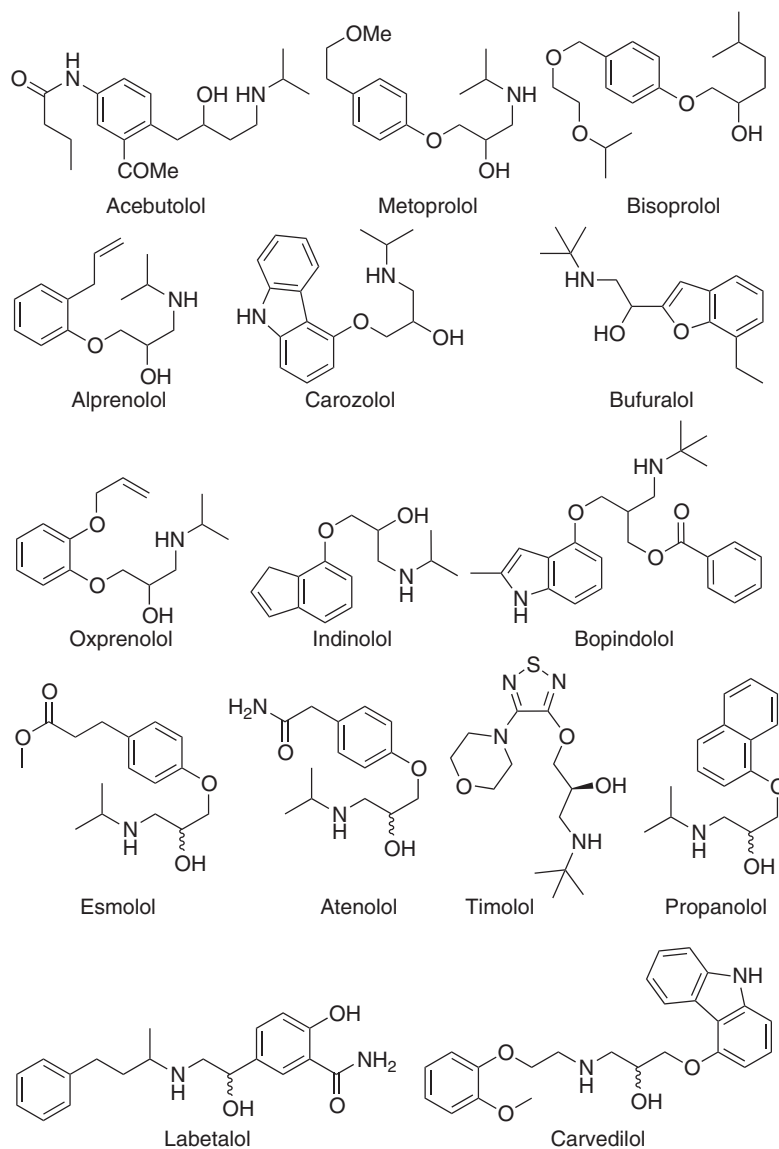


Figure 5.35 Structure of some β -blockers.

by Gabet-Giraud *et al.* [210] in 30 influent samples in France: acebutolol, atenolol, betaxolol, bisoprolol, metoprolol, nadolol, oxprenolol, propranolol, sotalol, and timolol. Three groups of molecules can be distinguished for the 10 β -blockers measured in the influent samples (see Table 5.7). The first group is constituted by acebutolol, atenolol, and sotalol. Those molecules are consistently quantified in influent wastewater at concentrations higher than 100 ng L^{-1} and up to 9800 ng L^{-1} . The second group is composed of bisoprolol, metoprolol, nadolol, and propranolol: these β -blockers are quantified in most of the influent

Table 5.7 Minima and maxima concentrations of β -blockers measured in influent and effluent of WWTPs.^{a)}

Compound	Influents (ng L ⁻¹)	Effluents (ng L ⁻¹)	Compound	Influents (ng L ⁻¹)	Effluents (ng L ⁻¹)
Acebutolol	910–9,867	32.0–3648	Betaxolol	1.8–108	5.8–27.9
Timolol	0.5–12.9	1.1–10.0	Propranolol	14.4–703	2.6–398
Metoprolol	4.6–473	15.8–435	Atenolol	990–8,384	35.5–2,257
Oxprenolol	0.9–21.0	1.1–28.0	Nadolol	3.4–983	3.3–98.0
Bisoprolol	44.0–429	8.4–220	Sotalol	129–3,200	128–3,334

a) Data taken from Ref. [210].

samples, but at concentration levels lower than the first group (up to 980 ng L⁻¹). Betaxolol, oxprenolol, and timolol are in the third group of molecules, which are less frequently quantified (30–60% of the samples) [210].

5.9 Lipid Regulators

Lipid regulators (such as bezafibrate, clofibric acid, fenofibric acid, atorvastatin, amlodipine, cilazapril, simvastatin, and enalapril) are massively prescribed for the treatment of high blood cholesterol levels (dyslipidemia) and other cardiovascular problems and have been prescribed, too, for the prevention or treatment of many other illnesses such as osteoporosis and postmenopausal complications. The main lipid regulators are statins (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin) and fibrates (bezafibrate, bezafibrate, clofibrate, fenofibrate, and gemfibrozil) (see Figure 5.36). Clofibric acid is an active metabolite of clofibrate, etofibrate, and etofyllin clofibrate which are drugs used as blood-lipid regulators. These substances are used to decrease the plasma concentration of cholesterol and triglycerides.

Statins are already metabolized, so despite their massive use, they do not represent a serious environmental problem, compared with fibrates [211]. For example, data of residual simvastatin monitored in activated sludge and trickling filter in WWTPs are in the 7–115 ng L⁻¹ range. The behavior of clofibrate and other similar fibrate drugs is that they are transformed into active metabolite clofibric acid. Clofibric acid is suspected of causing adverse effects on reproductive parameters such as spermatogenesis in fathead minnows [212] and it has been detected in sewage effluents, surface water, drinking water, and groundwater [213]. Clofibric acid has been also detected in STP influents and effluents, in German river waters, in Swiss lakes, and in groundwater wells [134, 147, 151, 214]. With respect to this acid, Díaz-Cruz *et al.* [23] have estimated a persistence of 21 years in waste-treatment residues or soils. Gemfibrozil (lipid regulator) was also detected in the low ng L⁻¹ range in the receiving waters of treated and untreated sewage outflows (see Table 5.8) [215].

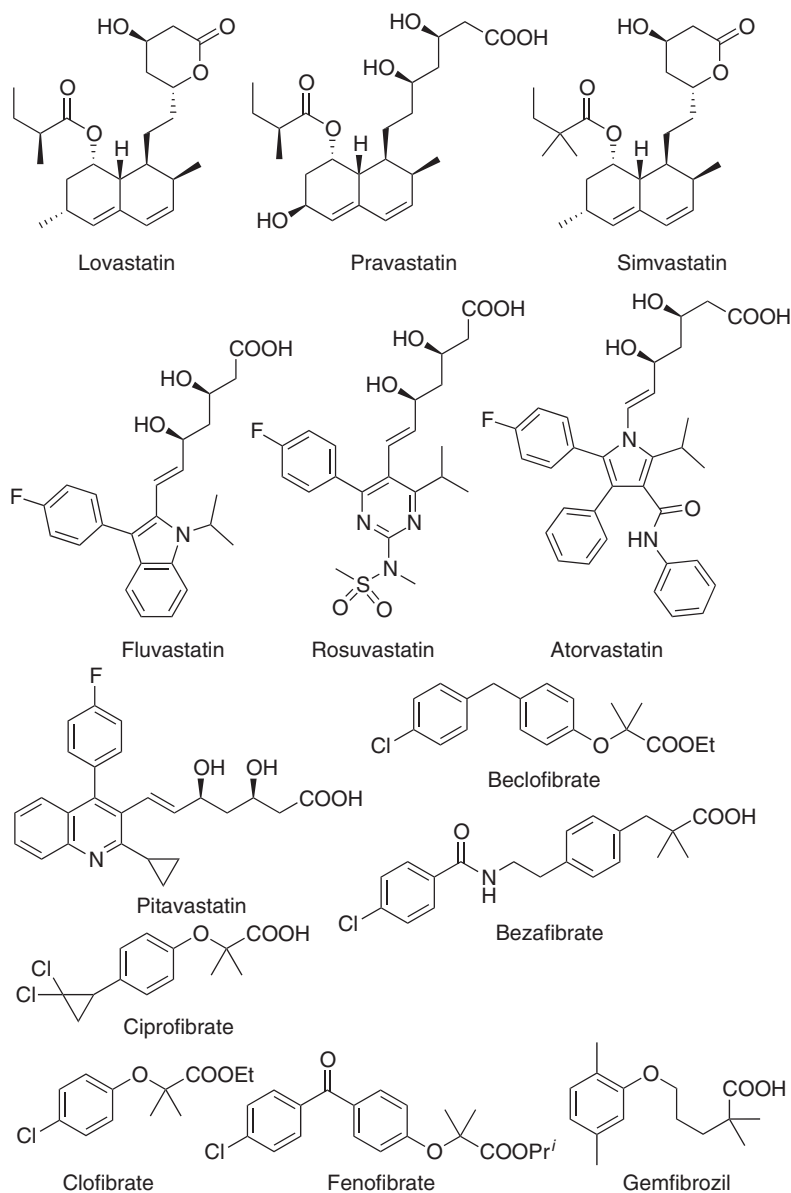


Figure 5.36 Main structure of statins.

5.10 β_2 -Sympathomimetic Drugs

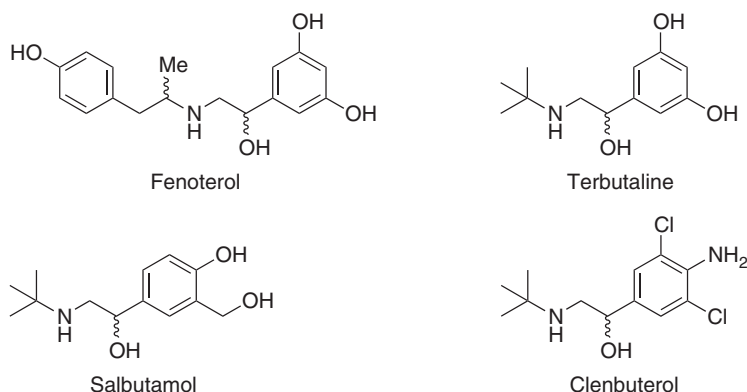
Sympathomimetic drugs (also known as adrenergic drugs) are stimulant compounds of the sympathetic nervous system. Sympathomimetic drugs are used to treat cardiac arrest and low blood pressure, among other ailments. Examples are fenoterol, terbutaline, salbutamol, and clenbuterol (see Figure 5.37). Prescription

Table 5.8 Concentrations of lipid regulators and metabolites in STP effluents as well as rivers and streams.^{a)}

Substances	STP effluents		Rivers and streams	
	LOD ^{b)}	Maximum ($\mu\text{g L}^{-1}$)	LOD ^{b)}	Maximum ($\mu\text{g L}^{-1}$)
<i>Lipid regulating agents</i>				
Bezafibrate	0.25	4.6	0.025	3.1
Gemfibrozil	0.050	1.5	0.010	0.51
Fenofibrate	0.050	0.03	0.010	n.d.
Etofibrate	0.10	n.d.	0.030	n.d.
Clofibrate	0.10	n.d.	0.030	n.d.
<i>Metabolites</i>				
Clofibric acid	0.050	1.6	0.010	0.55
Fenofibric acid	0.050	1.2	0.010	0.28

a) Data taken from Ref. [134].

b) Limit of detection, n.d.: not detectable.

**Figure 5.37** Chemical structure of some sympathomimetic β_2 agonist drugs.

sympathomimetic agents are commonly used especially for treating diseases such as asthma and narcolepsy.

The use of clenbuterol has been banned in meat since 1991 in the United States and since 1996 in the EU. The drug is banned due to health concerns about symptoms noted in consumers. These include increased heart rate, muscular tremors, headaches, nausea, fever, and chills. The United States and the EU prohibit the use of clenbuterol in food-producing animals.

Methods for its detection in biological specimens, drug preparations, the environment, and food and feed products have been reported [216]. They are based mainly on immunochemical, chromatographic, and mass spectrometric techniques, or on capillary electrophoresis. Typical concentrations of

Table 5.9 Concentrations of β -blockers, β_2 -sympathomimetics, and other drugs in STP effluents as well as in rivers and streams.^{a)}

Substances	STP effluents		Rivers and streams	
	LOD ^{b)}	Maximum ($\mu\text{g L}^{-1}$)	LOD ^{b)}	Maximum ($\mu\text{g L}^{-1}$)
<i>β-Blockers</i>				
Metoprolol	0.025	2.2	0.010	2.2
Propranolol	0.025	0.29	0.010	0.59
Nadolol	0.025	0.06	0.010	n.d.
Carazolol	0.025	0.12	0.010	0.11
Timolol	0.025	0.07	0.010	0.01
Betaxolol	0.025	0.19	0.010	0.028
Bisoprolol	0.025	0.37	0.010	2.9
<i>β_2-Sympathomimetics</i>				
Fenoterol	0.050	0.060	0.010	0.061
Terbutaline	0.050	0.12	0.010	n.d.
Salbutamol	0.050	0.17	0.010	0.035
Clenbuterol	0.050	0.08	0.010	0.050
<i>Psychiatric drugs</i>				
Diazepam	0.030	0.04	0.030	n.d.
<i>Antiepileptic drugs</i>				
Carbamazepine	0.050	6.3	0.030	1.1
<i>Cytostatic agents</i>				
Ifosfamide	0.010	2.9	0.010	n.d.
Cyclophosphamide	0.010	0.020	0.010	n.d.

a) Data taken from Ref. [134].

b) Limit of detection, n.d.: not detectable.

β_2 -sympathomimetics and other drugs have been detected in STPs effluents and the results are summarized in Table 5.9.

5.11 Antidiabetic Drugs

One pharmaceutical found in particularly high abundance in recent WWTP effluents and surface water studies is the biguanide metformin (see Figure 5.38).

**Figure 5.38** Chemical structure of metformin.

Metformin is one of the most widely prescribed antidiabetic drugs in the world and is also indicated as a potential treatment in various cancers [217] as well as in polycystic ovary syndrome.

Interactions between insulin signaling and steroidogenesis suggest potential endocrine-disrupting effects of metformin found in the aquatic environment. Metformin treatment induces significant upregulation of messenger ribonucleic acid (mRNA) encoding the egg-protein vitellogenin in male fish, an indication of endocrine disruption.

Recent work has revealed that metformin and its metabolite guanyurea are among the most abundant PCs introduced into the environment. It is found in WWTP effluents at concentrations of 1–47 $\mu\text{g L}^{-1}$ and in surface waters at concentrations from 0.06–3 $\mu\text{g L}^{-1}$ [218]–[222]. Although metformin is one of the most prevalent PCs in WWTP effluents [221], the impact of metformin on aquatic life has been explored only for its metabolic effects as they pertain to aquaculture [223] or drug screening [224], and the putative endocrine-disrupting effects of metformin have not been studied in aquatic organisms.

Trautwein and Kümmerer [225], investigated the biotransformation of the metformin and identified guanyurea as the main TP, which was formed from metformin by a two-fold dealkylation and an oxidative deamination. In a WWTPs, the concentration of metformin decreased from 56.8 $\mu\text{g L}^{-1}$ (influent) to 1.86 $\mu\text{g L}^{-1}$ (effluent), while the concentrations of guanyurea increased from 0.40 $\mu\text{g L}^{-1}$ (influent) to 1.86 $\mu\text{g L}^{-1}$ (effluent). Thus, they concluded that metformin is biotransformed in WWTPs into guanyurea.

5.12 X-Ray Contrast Drugs: Diagnostic Agents

Contrast media are used as diagnostic tools for capturing detailed X-ray images of soft tissues or organs, or components of circulatory system that are commonly used in diagnostic radiographic studies with several techniques such as intravenous urograms or computer tomography (brain and pulmonary angiograms). These drugs contain iodine atoms linked by covalent bonds to an organic structure. The presence of iodine atoms dramatically increases the absorption of X-rays in the body. Iodinated X-ray contrast media are highly hydrophilic substances that are widely used and eliminated almost non-metabolized.

The more widely used drugs are derivatives and analogs of triiodobenzoic acid, which differ in their side chains and which can contain carboxyl, amide moieties, or hydroxyl groups. The most commonly used contrast reagents are iopromide, iopamidol, diatrizoate, iomeprol, and iohexol (see Figure 5.39).

The normal dose administered to a patient is about 200 g, and the global consumption is approx. $3.5 \cdot 10^6 \text{ kg yr}^{-1}$. When these drugs are administered, 95% remains unmetabolized and is eliminated in urine and feces within 24 h. Once excreted, they become very resistant to biodegradation. The origin of this resistance is related to their high hydrophilicity (e.g., for iopromide $\log K_{ow} = -2.33$) and their non-ionic character. These properties make them quite persistent in the environment.

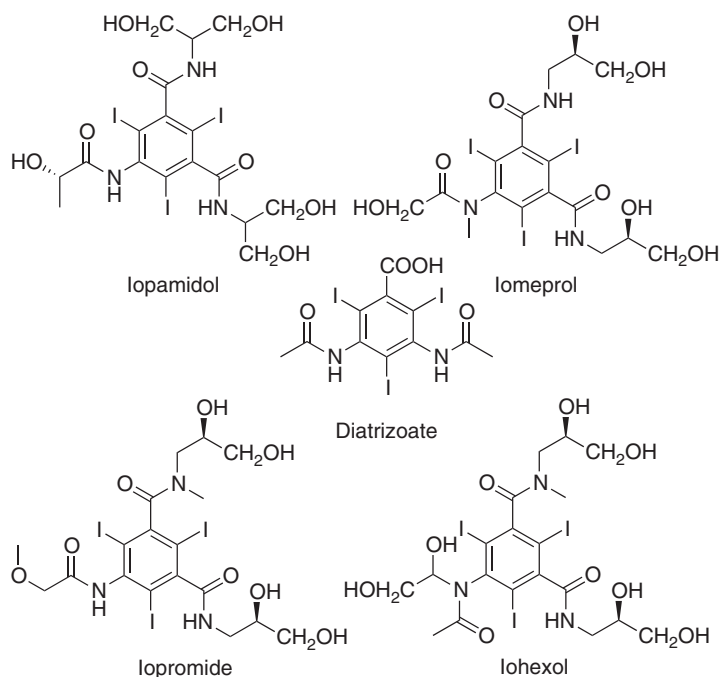


Figure 5.39 Structure of triiodobenzoic derivatives used as X-ray contrast drugs.

For example, the presence of iopromide in surface waters and wastewaters has often been reported as ranging from a few ng L^{-1} to as much as $10 \mu\text{g L}^{-1}$ in STPs and because of its common presence in wastewater it has been suggested as a potential indicator of contamination [226].

STP removal processes are usually ineffective and therefore these substances persist for long periods of time in the environment. As X-ray contrast media do not show biological activity, their presence might not represent a threat to public health [227]. Short-term toxicity of these molecules have shown that iopromide or its main metabolite does not have a toxic effect in luminescent bacteria, algae (*Scenedesmus subspicatus*), daphnids, or fish (*D. rerio*, *Leuciscus idus*) even at concentrations as high as 1 g L^{-1} [227].

5.13 Cytostatic PCs: Antineoplastics

Antineoplastic drugs (see Figure 5.40) are designed to kill cells that proliferate excessively, such as those found in pathological cancer conditions. Therefore, a similar effect on any other growing eukaryotic organisms is expected [228]. PCs belonging to this therapeutic class possess genotoxic, mutagenic, carcinogenic, teratogenic, and foetotoxic properties and can constitute (in their native form) from 14% to 53% of the administered drug excreted in urine [179].

Kosjek and Heath [229] reviewed the current literature regarding analytical methods, occurrence, and fate of cytostatic PCs. In hospital wastewater,

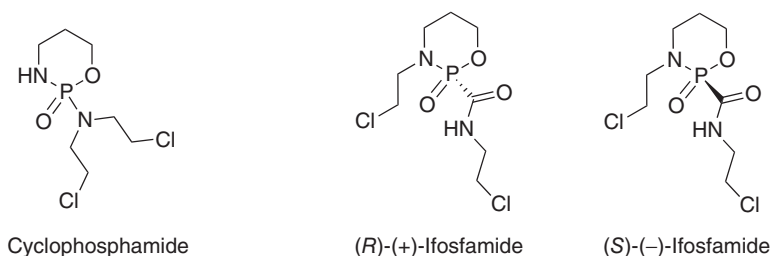


Figure 5.40 Chemical structure of some antineoplastic drugs.

concentrations up to $4.5 \mu\text{g L}^{-1}$ (cyclophosphamide) were detected, while in WWTP effluents and in surface water, the concentrations were found to be mainly in the lower ng L^{-1} range or even in the pg L^{-1} range. Gomez-Canela *et al.* [230] developed an analytical method with detection via LC/Orbitrap-MS to determine cyclophosphamide and epirubicin in aqueous samples down to 0.35 ng L^{-1} with SPE or alternatively, with direct injection down to 3 ng L^{-1} . Seira *et al.* [231] developed an analytical method for determining ifosfamide and cyclophosphamide in sewage sludge with limits of quantification (LOQ) down to 8.8 and $6.1 \mu\text{g kg}^{-1}$, respectively. Kosjek *et al.* [232] investigated the biodegradation and removal via UV of 5-fluorouracil and its product capecitabine by using ultraperformance liquid chromatography (UPLC)/ESI-Qq TOF-MS.

Cyclophosphamide was detected in hospital effluents at concentrations ranging from 19 ng L^{-1} to 4.5 g L^{-1} [233], in STP influents [234, 235] and effluents [234, 235] and in surface waters [27]. Other antineoplastic PCs detected to date have been on the order of ng L^{-1} .

5.14 Veterinary Drugs: Anthelmintics

Among PCs, anthelmintics are drugs that act against helminthic infections (i.e., caused by parasitic worms). Anthelmintics are administered to a wide range of veterinary- specific animals in agriculture and aquaculture, and comprise a large sector of the animal pharmaceutical industry. Research and development into anthelmintics has therefore demanded a very large share of the efforts put in for pharmaceutical development on animal health and is probably the only area of such research where efforts for and success in animal health exceed those concerning human health [236].

Anthelmintics have wide-ranging modes of action, including increasing calcium permeability, tubulin binding, proton ionophores, nicotinic and γ -aminobutyric acid agonists, and acetylcholinesterase inhibitors.

Very limited information is available on concentrations of anthelmintics in the environment [237]. Due to their wide applicability, anthelmintics are expected to have possible impacts on terrestrial and aquatic environments. These compounds can occur by excretion, either unchanged or as metabolites, which may retain parasitocidal activity [238]. In some cases, the anthelmintic metabolite was found to have a greater effect than the parent compound [239].

5.14.1 Classes of Anthelmintics

Anthelmintic PCs are categorized into eight groups by their mode of action against parasites, but primarily by their molecular structures. Therefore, they are divided, without mutual similarity [240], into:

- Benzimidazoles (I).
- Diphenylsulfides (II).
- Imidazothiazoles (III).
- Hexahydropyrazines (IV).
- Macrocyclic lactones (V).
- Salicylanilides (VI).
- Tetrahydropyrimidines (VII).
- Others (VIII).

Benzimidazoles (I) belong to the largest chemical family used to treat endoparasitic diseases in domestic animals. This group includes benzimidazol carbamates, thiabendazole analogs, triclabendazole and pro-drug netobimin (NETO), a phenylguanidine derivative, which is rapidly converted into albendazole (ABZ) *in vivo*. The individual members of methyl benzimidazol-2-yl-carbamates ABZ, fenbendazole (FBZ), flubendazole (FLU), mebendazole (MBZ), oxfendazole (OFZ), and oxibendazole are replaced with some particular substituents (alkyl- and arylsulfanyl, benzoyl or arylsulfinyl, alkyl- and aryloxy) at position 5(6)- of the parent nucleus, and isopropyl benzimidazol-6-ylcarbamate, cambendazole is substituted with 1,3-thiazole at position 2- of benzimidazole heterocycle [241]. Figure 5.41 depicts the molecular structure of commercially available anthelmintics.

Diphenylsulfides (II) include bithionol (BIT) and febantel (FEB). Structurally, FEB is related to benzimidazoles. As it is, at least partially, metabolized to fenbendazole (FBZ) and OFZ *in vivo*, it is also categorized as a probenzimidazole agent.

Levamisole is marketed as the hydrochloride salt belonging to a class of synthetic imidazothiazole (III) derivatives (see Figure 5.42).

Diethylcarbamazine, piperazine, and praziquantel belong to the hexahydropyrazine (IV) group of anthelmintics (see Figure 5.43). Diethylcarbamazine is formulated as the water-soluble citrate salt containing 51% by weight of the active base. Piperazine is a weak base with a pK_a of 9.8. Praziquantel is a pyrazinoisoquinoline derivative, whose (–)-isomer is responsible for most of the drug's anthelmintic activity.

Avermectins are disaccharide derivatives of a novel class pentacyclic, 16-membered lactones, the macrocyclic lactone (V) group of anthelmintics (see Figure 5.44). Abamectin is a mixture of avermectins containing more than 80% avermectin B1a and less than 20% avermectin B1b. The *a* and *b* series are *sec*-butyl and isopropyl homologs, respectively. These two components, B1a and B1b, have very similar biological and toxicological properties. Ivermectin is a semi-synthetic 22,23-dihydro analog of abamectin, an insecticide developed for crop management. To this group of avermectines also belong 6-cyclohexyl

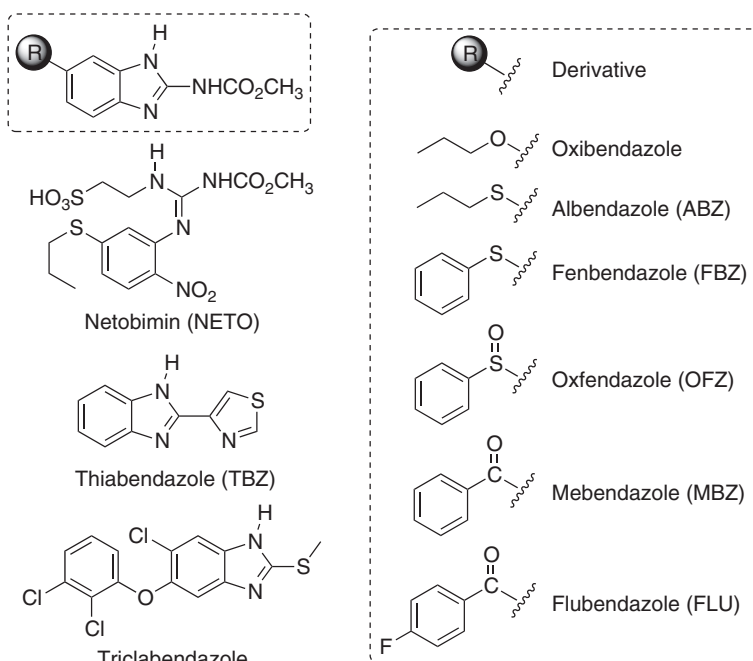


Figure 5.41 Chemical structure of some commercially available anthelmintic benzimidazoles (I).

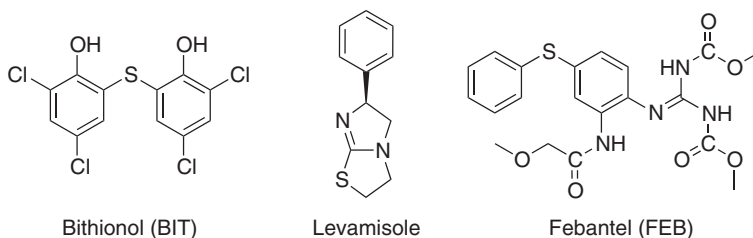


Figure 5.42 Chemical structure of some commercially available anthelmintics diphenylsulfides (II) and imidazothiazole (III) groups.

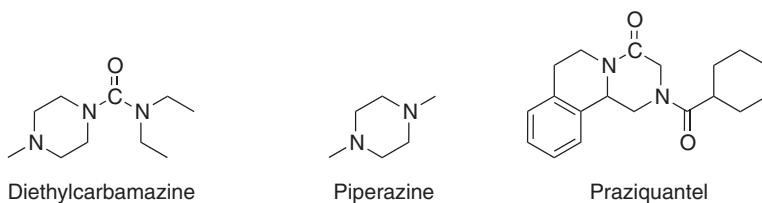


Figure 5.43 Chemical structure of some commercially available anthelmintics hexahydropyrazine (IV).

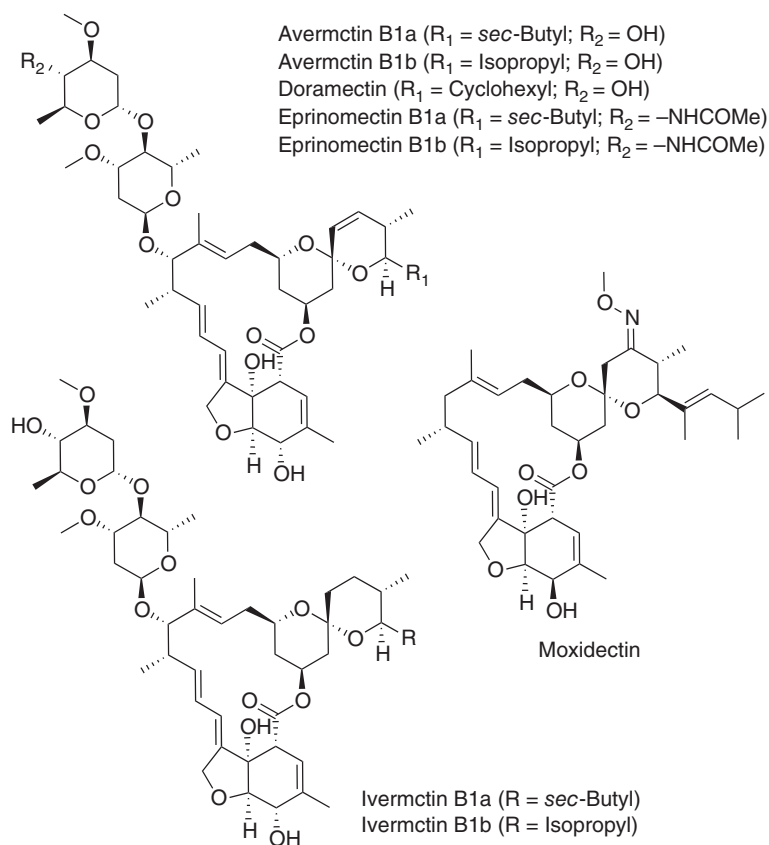


Figure 5.44 Chemical structure of some commercially available anthelmintics macrocyclic lactone (V) group.

derivatives doramectin and eprinomectin, which is avermectin B1 substituted with an amino sugar.

The salicylanilide group of anthelmintics is halogenated salicylanilide derivatives. These include closantel, oxclozanide, rafoxanide, niclosamide, and their salts (see Figure 5.45).

The tetrahydropyrimidine group of anthelmintics is composed of morantel (MOR) (morantel tartrate) and pyrantel (PYR) pamoate (pyrantel embonate) (see Figure 5.45).

The last group of anthelmintics is characterized by a biphenyl structure, and includes suramin (SUR), niclofolan (NIF), and phenothiazine (see Figure 5.46), which have different molecular structures and modes of action. SUR is a symmetric molecule, in the center of which is *N,N*-disubstituted urea, substituted with two connected *N*-phenylcarbamoyl groups substituted at the end with naphthalene-1,3,5-trisulfonic acids.

When a patient is administered with an anthelmintic drug, it usually contains six sodium ions that form a salt with the six sulfonic acid groups. Anthelmintic

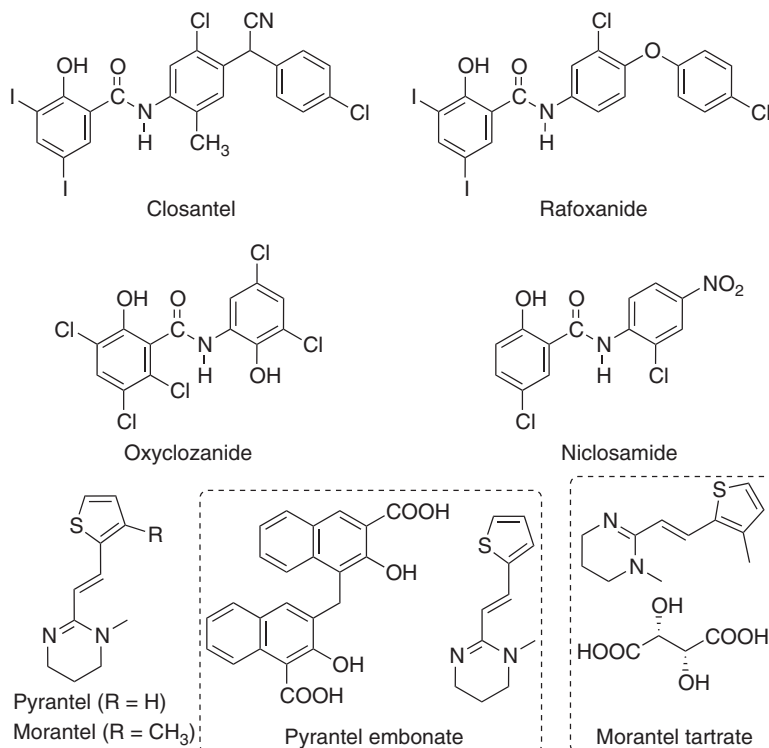
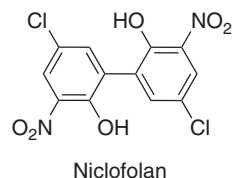


Figure 5.45 Chemical structure of anthelmintics salicylanilide (VI) and tetrahydropyrimidine (VII) groups).

Figure 5.46 Chemical structure of niclofolan (NIF).



substance NIF is hydroxy-, chlor-, and nitro-substituted biphenyl. Phenothiazine is related to the thiazine-class of heterocyclic compounds.

Anthelmintics are insoluble or slightly soluble in water, and selected solubility and pK_a values are summarized in Table 5.10. Log K_{ow} values are relatively high for almost all anthelmintics, indicating that these compounds are strongly adsorbed to sediment/soils and therefore not mobile [241, 242].

5.14.2 Anthelmintics in the Environment

Only limited data are available concerning the environmental fate of the anthelmintic drugs. The majority of papers dealing with the transformation of anthelmintics are those about metabolic pathways in living organisms [241].

The environmental fate of anthelmintic drugs and their metabolites strongly depends on their physicochemical properties. Before entering the environment,

Table 5.10 Physicochemical properties of selected anthelmintics.^{a)}

Anthelmintic	Water solubility	
	(mg L ⁻¹)	pK _a
Albendazole	10	3.37, 9.93
Ricobendazole	62	3.5, 9.8, 7.8
Fenbendazole	0.01–0.04	
Flubendazole		3.6, 9.6
Mebendazole	10	3.5
Thiabendazole		4.7, 12
Piperazine		5.68, 9.82
Moxidectin	4	

a) Data taken from Ref. [[240], and references therein].

PCs can be metabolized in living organisms to phase I or phase II metabolites. Phase I reactions are usually oxidation, reduction, or hydrolysis, and the metabolites are often more reactive and more toxic than the parent drug. Phase II reactions often result in inactive compounds [243].

Anthelmintics do not occur in the environment as single contaminants, but rather as complex mixtures with other PCs and contaminants. The interactive effects of compounds could increase or decrease the potential effects in the environment.

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6

Illegal Drugs, Occurrence, and Fate in Environment

6.1 Introduction

Illicit drugs (IDs) are the latest group of emerging pollutants to be identified in the aquatic environment, which are receiving special attention [1]. Similar to PCs, many of the IDs have potent pharmacological effects and their presence in complex mixtures may have toxic effects.

Although it has been known for many decades that IDs and their metabolites are excreted in urine, feces, hair, and sweat, the ramifications for the environment were basically ignored until 1999 [2], when the scope of concerns surrounding pollutants in the environment was expanded to include IDs. Until the mid-2000s, the emerging study of PCs on the environment inexplicably excluded the contributions by IDs to the overall environmental loadings. However, the actual magnitude of these contributions is unknown and can only be roughly estimated. The potential for IDs to enter the environment via a wide array of pathways should not greatly differ from that of PCs used in the practice of medicine.

IDs have been indicated as emerging contaminants detected in wastewater from municipal STPs, surface as well as in drinking water in several European countries and in the United States. As PCs, the main source of contamination by IDs is human consumption. The residues of drugs of abuse persisting in consumers' urine can reach STPs in detectable amounts, escaping degradation. As a result, these substances are still detectable in treated water and contaminate the receiving surface waters.

Wastewater analysis was first introduced to monitor the environmental contamination caused by PCs and to assess the effectiveness of WWTPs for their removal [3]. Subsequently, sources, behavior, and fate of therapeutic drugs in the environment have been extensively studied [4, 5]. Recently, some investigations have shown that the same methodology can be used to measure IDs in wastewater. In fact, the amounts of IDs consumed worldwide are comparable with those of therapeutic drugs, as millions of individuals are current users of cocaine, heroin, amphetamine-like stimulants, marijuana, and other drugs [6].

Environmental concentrations of these drugs are low, but risks for human health and the environment cannot be excluded. Levels of residues in untreated wastewater have been used to estimate ID consumption in the population.

Perhaps, the first published indication that IDs might be pervasive contaminants of the environment was a 1987 FBI study performed in response to a newspaper report 2 years earlier that cocaine was present in general circulation and could be purchased [7]. Analogous surveys of ambient ID contaminants have been attempted for the first time for sewage wastewaters, [8] surface waters [9], air [10], sewage sludge [11], biosolids [12], and most recently drinking water [13].

The first investigations of IDs in the environment were conducted in the United States in 2004 for amphetamines, and in Italy in 2005 for cocaine and its main urinary metabolite (Benzoylecgonine). Several other substances were later measured in water and air, including cannabinoids, cocaine and its metabolites, opioids, amphetamines, ephedrine, ketamine, lysergic acid diethylamide, and some related opioid PCs.

Several drugs can be detected in wastewater from municipal STPs [14–17], and some are even measurable in surface waters [18–20]. Moreover, the potential of IDs to escape degradation in DWTPs and enter potable water was recently evaluated in Spain [13].

A first report by Zuccato *et al.* [9] that kilograms of cocaine residues travel daily down the Po river (Italy) received worldwide media coverage, suggesting widespread interest and concern for these findings. Monitoring has been subsequently extended to other common drugs of abuse, such as opioids, amphetamines, and cannabis derivatives, and to some related opioid PCs, such as codeine and methadone, which have been detected in wastewater and surface water in several countries in Europe.

Cocaine, methamphetamine, 3,4-methylenedioxyamphetamine and MDMA (ecstasy) all have strong activities, and their presence as complex mixtures in surface waters (together with residues of many therapeutic drugs) might in fact have biological effects even at low environmental concentrations [21].

6.2 What is an Illicit Drug?

Any discussion regarding IDs can become confused by the ambiguity as to what exactly defines an IDs. Confusion stems from the fact that IDs are not limited exclusively to illegal drugs with no medical use. IDs can also include active pharmaceutical ingredients having valuable therapeutic uses (e.g., morphine and oxycodone). They can also include active ingredients that are banned from all use under various international conventions or national laws, as they are deemed as having no use in health care [22].

IDs are those whose non-medical use is prohibited by the law, and mainly belong to the class of opiates, are cocaine, cannabis, amphetamine-type substance (ATS), and so on.

The term “illicit drug,” while widely used, is not accurate in the sense that most of the widely known abused drugs have genuine medical uses as licit pharmaceuticals. A variety of terms are loosely used in discussions regarding IDs. Major terms include street drugs, designer drugs, club drugs, drugs of abuse, recreational drugs, clandestinely produced drugs, and hard and soft drugs. The term

“research chemicals” has been used by the clandestine laboratory community as an alternative term for designer drugs. The term “designer” drug was first applied in the 1980s to designate various analogs of fentanyl and then gained popularity when MDMA was introduced to the black market; but, perhaps the most notable first “designer” drugs were introduced in the 1920s (e.g., dibenzoylmorphine and acetylpropionylmorphine) [22].

The “United Nations Office on Drugs and Crime” (UNODC) does not recognize any distinction between the chemical identity of licit and IDs, only the way in which they are used.¹ The term “illicit” refers to the way in which these drugs are manufactured, formulated, distributed, acquired, and consumed and by the fact that they are being used for non-medical purposes. Therefore, this definition allows the inclusion of legal PCs, that is, when they are manufactured, formulated, distributed, trafficked, or used illegally or diverted from legal sources.

The lines of demarcation between licit and IDs have become blurred. As a case in point, prescription analgesic opioids (which are controlled prescription drugs) have now superseded heroin and cocaine in the United States leading to fatal drug overdoses [23]. Indeed, the use of certain licit drugs for non-medical purposes has recently surpassed the use of IDs. For example, of the top 10 drugs that are misused by high-school seniors in the United States, seven were legal prescription or over-the-counter medications [22].

6.2.1 Differences Between Licit and Illicit Drugs as Environmental Contaminants

The primary factor that distinguishes licit drugs (registered) from illicit drugs is that the latter have no legal (registered) uses, whereas the former may be illegally used. With respect to understanding their overall significance in the environment, seven aspects of IDs use contrast sharply with legitimate pharmaceutical use:

- For most ID, no accurate quantitative data are available on their production or use. For regulated PCs, sales figures and regional real-time prescription data can be used in models to calculate predicted environmental concentrations; these values can then be compared with measured environmental concentrations.
- Although the chemical identities for the core group of IDs are known, an ever-increasing number of new drugs (such as structural analogs with minor modifications of regulated PCs and of previously known IDs) can elude detection by forensic laboratories for years before they are noticed and identified. The myriad numbers of designer drugs and constant synthesis of new ones will pose challenges for mass spectrometrists in the coming years and introduce great uncertainty to the true scope of synthetic chemicals that actually contaminate the environment. Although many of these unique chemicals are probably produced in relatively small quantities, the fact that they belong to relatively few chemical classes may mean that they share comparatively few mechanisms of biological action. This increases the probability of biological effects

1 <http://www.unodc.org/unodc/en/illicitdrugs/definitions/index.html>.

resulting from dose (or concentration) “additivity.” When multiple chemical toxicants in a mixture share the same mechanism of biological action, the dose of each toxicant can add to that of the others. Even if the concentration of each individual toxicant is below an effect threshold, the mixture’s combined dose can elicit effects as if it constitutes a single larger dose.² Dose additivity is distinct from potentiation, where a chemical having no biological action of its own can enhance the action of another. Some designer drugs are highly potent, having extremely low effective doses (e.g., in the range of 1 µg per human use), and this has environmental implications, especially for aquatic exposure. As examples, *cis*-3-methylfentanyl and β-hydroxy-3-methylfentanyl (as with carfentanyl, a large animal tranquilizer) are extraordinarily potent designer drugs, being 3–5 orders of magnitude more potent than morphine.

- Drugs manufactured via illicit routes are commonly contaminated with unintended impurities and intended adulterants. These are often present at extremely high levels³ and are often more toxic than the sought-after drug ingredient.
- The manufacture of IDs (particularly methamphetamine) can cause extensive ecological damage [24, 25].
- The primary interest in residues of IDs in the environment has not been their occurrence in the environment as contaminants, but rather their presence in sewage (mainly untreated raw sewage) for use as a tracking tool to calculate levels of their community-wide consumption.
- Compared with PCs, much less is known about the toxicology (including pharmacokinetics), especially in the aquatic environment, of many IDs (particularly designer drugs); for human research, there are added legal and ethical difficulties in studying them. Knowledge of the scope of bioactive metabolites and the extent of reversible conjugation is comparatively limited.
- Numerous measures are routinely implemented to reduce the entry of licit PCs into the environment and moderate their potential for adverse effects [26]. With IDs, pollution prevention measures are straightforward but more difficult to implement – namely, discourage their manufacture, distribution (e.g., via unapproved “rogue” Internet pharmacies), and end use.

The rate of introduction of new PCs with potential for abuse and of new illicit substances precludes any definitive comprehensive worldwide compilation of such chemicals. The international narcotics control board maintains three major listings:⁴

Yellow list: Narcotic drugs under international control.

Green list: Psychotropic substances under international control.

Red list: List of chemicals frequently used in the illicit manufacture of narcotic drugs and psychotropic substances under international control.

² A phenomenon informally referred to as “something from nothing.”

³ Sometimes more than half of the total mass, as opposed to mg kg⁻¹ (ppm) levels for impurities in registered medicines.

⁴ International narcotics control board: narcotic drugs, psychotropic substances, and precursors. <http://www.incb.org>.

The scope of chemicals that could be considered illicit can be viewed in terms of the following categories of medical efficacy:

- No known medical use (which are illegal in all circumstances according to various conventions) (e.g., benzylpiperazine; or heroin in the United States).
- Limited established medical use but also manufactured illegally and used primarily for non-medical purposes (e.g., Methamphetamine).
- Firmly established with wide medical use but diverted for illegal use (e.g., theft; illegal prescription such as via unapproved Internet pharmacies).
- Firmly established wide medical use and legally obtained, but for non-medical use (e.g., doctor/hospital shopping).
- Biological action similar to prescription drugs but synthesized as analogs, which are not individually and explicitly categorized as illegal; examples include the numerous analogs of phosphodiesterase type-5 inhibitors.

All of these categories tend to include primarily drugs with high potential for abuse or recreational use.

6.3 Classes of Illicit Drugs

The types of drugs commonly abused are categorized in various ways, depending on their origin and biological effect. They can either be naturally occurring, semisynthetic (such as analogs of substances extracted from natural materials) or synthetic (produced entirely by laboratory synthesis and manipulation).

While there are a number of IDs that are synthetic, three major drugs originate from natural sources: tetrahydrocannabinol, which is the active ingredient of cannabis (*Cannabis sativa*); opium, morphine, and heroin produced from the opium poppy (*Papaver somniferum*); and cocaine produced from the coca plant (*Erythroxylum*) spp [27].

The primary categories are opiates, other central-nervous-system depressants (sedative-hypnotics), central nervous system stimulants, hallucinogens, and cannabinoids.

6.3.1 Opiates

Opiates, the generic name given to a group that includes naturally occurring drugs derived from the opium poppy (*Papaver somniferum*), include morphine and codeine; semi-synthetic substances such as heroin and opioids (opiate-like), and wholly synthetic products such as methadone, pethidine, and fentanyl (see Figure 6.1). Opiates depress the central nervous system and are used therapeutically as analgesics (painkillers), as cough suppressants, and against diarrhea; in non-medical use as euphorants as a means of reducing anxiety, boredom, and physical or emotional pain.

6.3.1.1 Opiates in the Environment

Untreated wastewater of WWTPs in Italy, Spain, Switzerland, the United Kingdom, Belgium, Germany, and Ireland contained morphine and

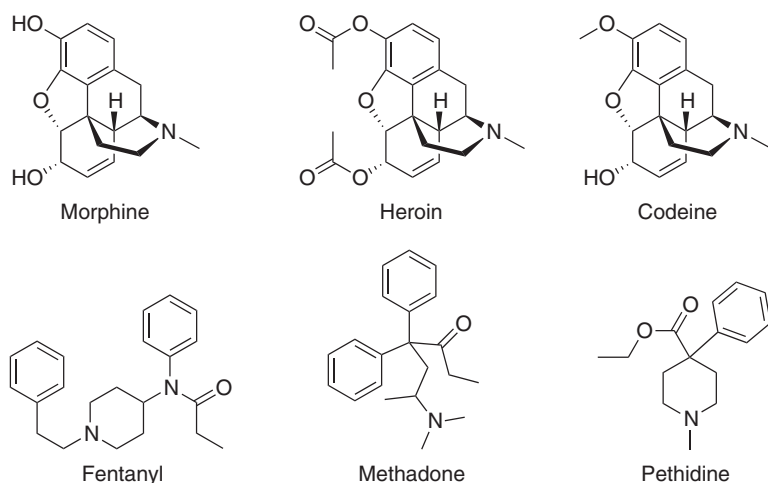


Figure 6.1 Chemical structure of main opiate-type substances.

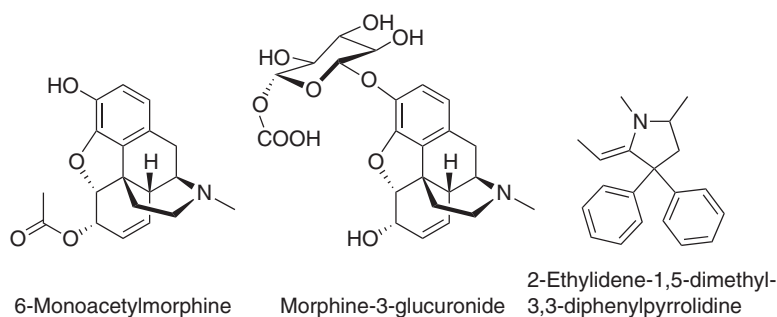


Figure 6.2 Chemical structure of main opiate metabolites.

6-monoacetylmorphine (see Figure 6.2).⁵ Morphine median concentrations were lower than 100 ng L^{-1} in Italy and Spain [14, 17, 28], but higher in Germany, Switzerland, and England (approx. 300, 200, and 600 ng L^{-1} , respectively), probably in relation to higher consumption of therapeutic morphine in these countries [15, 29]. Levels of 6-acetylmorphine were in the range of $8.6\text{--}14 \text{ ng L}^{-1}$. Trace amounts of morphine-3-glucuronide (up to 5.1 ng L^{-1}) were also found in some WWTPs (see Fig. 6.2) [15]. Opiate PCs such as codeine, methadone, and its major metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine were also measured in Italy, Switzerland, Germany, and Spain (see Figure 6.2) [14, 28, 29].

6.3.2 Other Central Nervous System Depressants

This category, also referred to as sedative-hypnotics, includes barbiturates, non-barbiturate depressants, and benzodiazepines. These can be used therapeutically as anesthetics, and anticonvulsants, as well as in the treatment of tension, anxiety, insomnia, and certain psychiatric illnesses. The first

⁵ A metabolite specific for heroin.

major type of group in this category to be manufactured was the barbiturate group, a synthetic PC, which since the 1960s has largely been replaced therapeutically by benzodiazapines such as diazepam (valium) (see Figure 5.31 in p. 130).

Benzodiazapines and non-barbiturate sedatives such as methaqualone appear regularly on the illicit market and are used for sedation and for pleasurable intoxication, often in combination with alcohol. Barbiturates are powerful central-nervous-system depressants.

6.3.3 Central Nervous System Stimulants: Cocaine

Central nervous system stimulants include naturally occurring plants such as coca (*Erythroxylum coca*), khat, and betel nuts (which are not under international control), products extracted from the leaf of the coca plant and wholly synthetic substances in the form of amphetamine and amphetamine-type compounds. Cocaine has some therapeutic value as a local anesthetic, while some synthetic stimulants are used as anorectics. Cocaine comes in two chemical forms: hydrochloride salt, which is the water-soluble white or off-white powdered form of cocaine, and cocaine alkaloid, a free base that is lipid-soluble. This drug is extracted from the leaves of the coca plant. Crack is cocaine that has been further processed with ammonia or sodium bicarbonate.

Cocaine acts as a powerful stimulant of the central nervous system, with additional effects that include local anesthesia and vasoconstriction. Cocaine prevents neurotransmitter (dopamine, norepinephrine, serotonin, and acetylcholine) reuptake at presynaptic nerve terminals, thereby increasing the amounts of neurotransmitters available for stimulation of sympathetic nerves [30]. The euphoria related to cocaine use is a result of accumulation of dopamine and serotonin in the mesolimbic and mesocortical areas of the brain [31]. According to Ambre [32], 45% of cocaine is excreted in urine by the human body mainly as benzoylecgonine and only a minor part is excreted as the parent drug (see Figure 6.3).

6.3.3.1 Cocaine in the Environment

Studies have documented the presence of the parent compound cocaine and its metabolites (benzoylecgonine, norbenzoylecgonine, norcocaine, cocaethylene, and ecgonine methyl ester) in influent wastewater [9, 14–18, 29, 33–45].

Parameters such as drug concentration, water flow rate, and population of medium-size Italian cities were used to estimate local cocaine consumption [9].

6.3.4 Central-Nervous-System Stimulants: Amphetamine-Type Substances (ATSs)

ATSs comprise two groups of compounds:

- 1) The amphetamine group (e.g., amphetamine, methamphetamine).
- 2) The ecstasy group (e.g., MDMA and analogous compounds).

Amphetamine-group substances account for more than three-quarters of ATS and currently demand the most attention of all the synthetic IDs (see

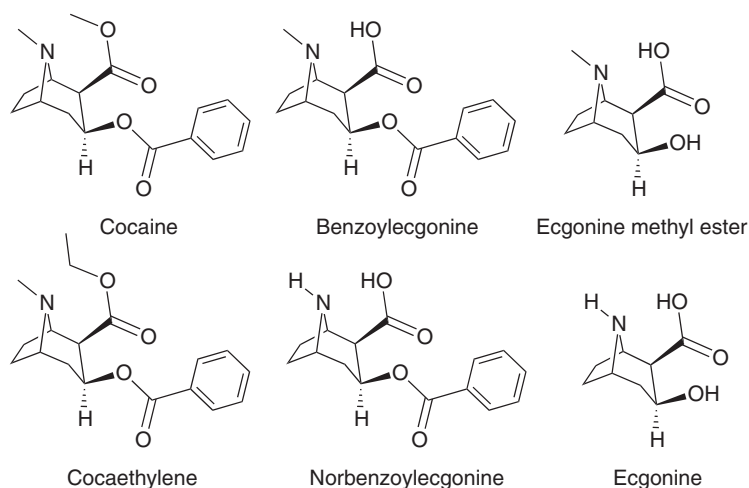


Figure 6.3 Structure of the parent compound cocaine and its metabolites.

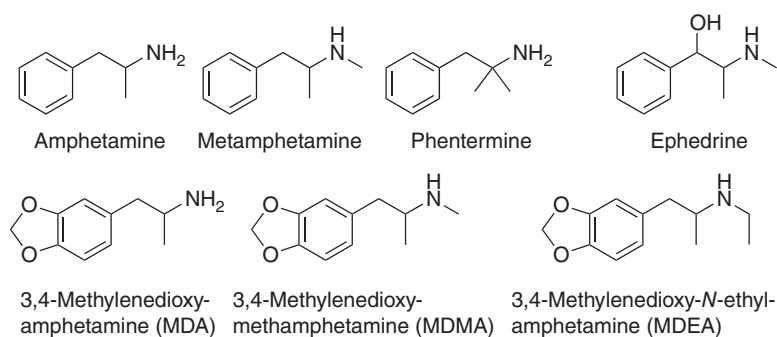


Figure 6.4 Chemical structure of main amphetamine-type substances (ATS).

Figure 6.4).⁶ Methamphetamine continues to be the most widely manufactured ATS and accounted for 68% of the amphetamine groups as per 2006 estimates.^{7,8}

In comparison to the plant-based drugs (e.g., heroin and cocaine), methamphetamine and ATSs are relatively easy to manufacture in clandestine laboratories from commonly available chemicals [46, 47].

6 EMCDDA (European Monitoring Centre for Drugs and Drug Addiction). 2007. Annual Report: The state of the drugs problem in Europe. <http://www.emcdda.europa.eu/html.cfm/index44682EN.html>.

7 UNODC (United Nations Office on Drugs and Crime). 2008. World Drug Report. United Nations publication. http://www.unodc.org/documents/wdr/WDR_2008/WDR_2008_eng_web.pdf.

8 UNODC (United Nations Office on Drugs and Crime). 2008. Amphetamines and Ecstasy: Global ATS Assessment. United Nations publication. <http://www.unodc.org/documents/scientific/ATS/Global-ATS-Assessment-2008-Web.pdf>.

The clandestine manufacture of methamphetamine frequently involves pseudoephedrine and/or ephedrine as the precursor. This is a relatively simple procedure that produces the more pharmacologically potent (+)-methamphetamine [48, 49]. In south-east Asia, ephedrine or pseudoephedrine are commonly converted into chlorephedrine, which is then reduced to methamphetamine (using the so-called Emde method). In Australia and the United States, the reduction of pseudoephedrine or ephedrine with hydroiodic acid and red phosphorous (the Nagai method) or its variants are favored [50, 51]. Variations of the hydroiodic/red phosphorus pathway include the use of iodine, water, and red phosphorus, which is known as the “Moscow” method, or iodine and hypophosphorus acid [51]. Phenyl-2-propanone (P2P) is another key precursor, as it can be converted into either methamphetamine or amphetamine using a wide variety of reagents. One favored process, called the Leuckart reaction, uses P2P as a precursor and formamide or *N*-methylformamide for amphetamine or methamphetamine synthesis, respectively. Less common methods for drug manufacture in Australia involve the use of nitroethane in the conversion of benzaldehyde into amphetamine or methamphetamine and in the conversion of piperonal into MDMA, the use of safrole in the production of MDMA or 3,4-methylenedioxyamphetamine, and the conversion of phenylacetic acid into P2P under conditions that lead to its contamination with dibenzyl ketone (see Figure 6.5) [47].

All synthetic methods produce reaction by-products as well as the target drug. In some instances, the by-products are characteristic of the synthetic procedure that was used, in which case the by-products are called “route-specific.” Forensic chemists are often able to detect route-specific by-products in both residues from clandestine laboratories, and can thereby infer the route of manufacture.

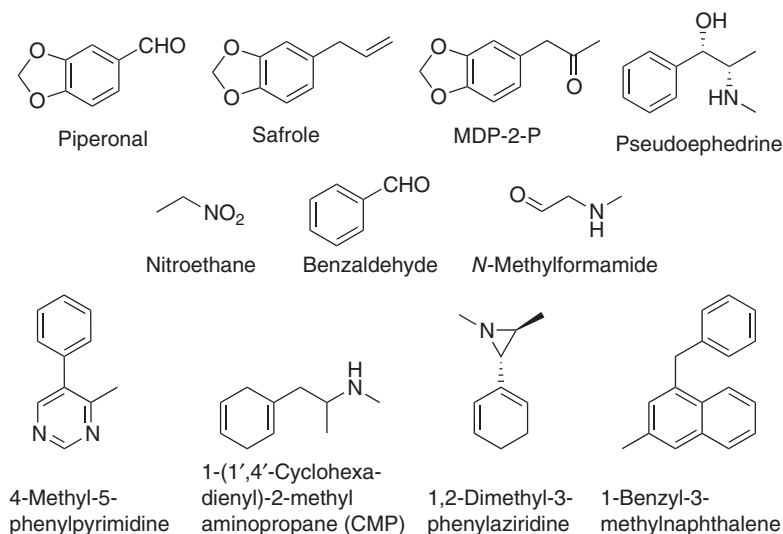


Figure 6.5 Chemical structure of some precursors and by-products in illicit drug manufacture.

A route-specific by-product in the Leuckart synthesis of amphetamine is 4-methyl-5-phenylpyrimidine [52]. *N*-formylamphetamine and *N*-formylmethamphetamine are also by-products in the Leuckart method, but they are not route-specific [53]. However, 1-(1',4'-cyclohexadienyl)-2-methyl aminopropane (CMP) is a route-specific by-product in the clandestine manufacture of methamphetamine by reduction of ephedrine or pseudoephedrine in the presence of ammonia and excess lithium [54, 55]. The synthetic route is similar to the Birch reduction. Route-specific by-products for the Nagai method and its variants are 1-benzyl-3-methylnaphthalene and 1,3-dimethyl-2-phenylnaphthalene, while P2P and 1,2-dimethyl-3-phenylaziridine are also present, which are not route-specific [53].

6.3.4.1 Amphetamine-Type Substances in the Environment

Various authors have investigated the occurrence of amphetamine-like stimulants, such as amphetamine [14, 16, 17, 34, 36, 38, 42, 45, 56], methamphetamine [14, 16, 17, 38, 42, 45, 56–58], MDMA [14, 16, 17, 36, 38, 42, 45, 57, 58], 3,4-methylenedioxy-*N*-ethylamphetamine [14, 16, 36, 38], 3,4-Methylenedioxyamphetamine, [14, 16, 36, 38] and ephedrine [17, 36, 45] in wastewater.

However, only amphetamine, methamphetamine, MDMA, and ephedrine consumption have been estimated from amphetamine-like stimulant residues present in wastewaters [15, 16, 43–45].

6.3.5 Hallucinogens

Hallucinogens include naturally occurring substances such as psilocybine (from the *Psilocybe mexicana* mushroom), mescaline (from the peyote cactus) and semi-synthetics such as lysergic acid diethylamide and synthetics such as phencyclidine (see Figure 6.6). Besides some traditional uses and for some rare therapeutic use in psychiatry, hallucinogens are taken illicitly for their mind-altering or “psychodelic” effects. Even in small doses, lysergic acid diethylamide causes perceptual distortions of time and place, visual hallucinations, and synesthesia.⁹

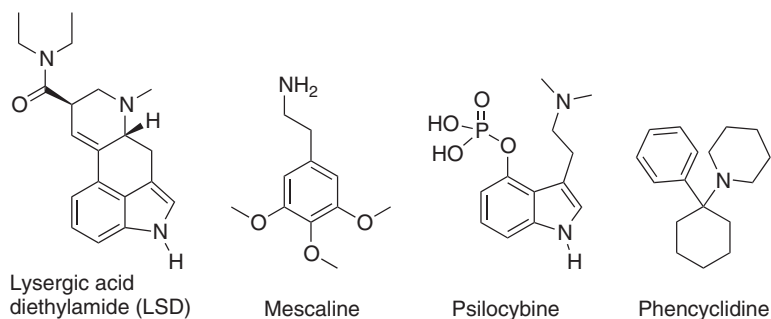


Figure 6.6 Chemical structure of main hallucinogen substances.

⁹ A merging of the senses such that sounds are “seen” and colors are “heard.”

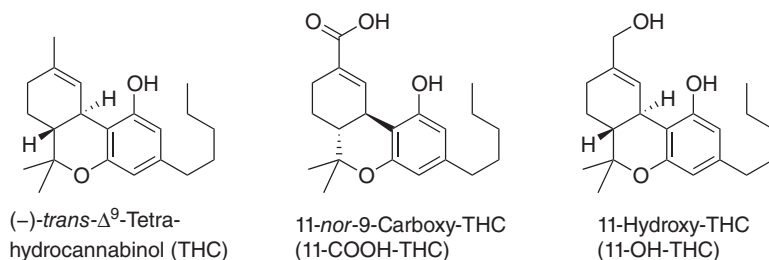


Figure 6.7 Chemical structure of main cannabinoids substances.

6.3.6 Cannabis

Cannabis has by far the highest rates of prevalence globally. It is consumed mainly as marijuana (the dried flowering tops of the *Cannabis sativa* plant), as hashish (resin from the plant), or as an oil extracted from the resin. Cannabis is a sedative, but it also has hallucinogenic effects that may last up to several hours. The principal psychoactive ingredient is THC, but a wide variety of THC levels exists within the various strains of cannabis that are now grown. Cannabis is soluble in fat, metabolizes very slowly and it remains in the body for up to one month after consumption.

6.3.6.1 Cannabis and its Metabolites in the Environment

Residues of the active principle in cannabis, (-)-*trans*- Δ^9 -tetrahydrocannabinol (THC), and its metabolites 11-*nor*-9-carboxy- Δ^9 -tetrahydrocannabinol (11-COOH-THC) and 11-hydroxy- Δ^9 -tetrahydrocannabinol (11-OH-THC) have been documented in untreated wastewater of several municipal WWTPs (see Figure 6.7). Average levels of 11-COOH-THC were 62, 91, and 159 ng L⁻¹ in Milan, Lugano, and London, respectively [15], and 15.3 and 37.8 ng L⁻¹ in Spain [17, 28], where the same authors also found measurable levels of THC (11.3–18 ng L⁻¹) and 11-OH-THC (30.7 ng L⁻¹).

6.4 Analytical Methods for Detecting of Illicit Drugs

The first step toward measuring IDs in the environment is the preconcentration of analytes operated mainly by SPE. Considering the complexity of the environmental matrices and the low concentrations of the analytes, MS is the most powerful technique to detect IDs with both high specificity and accuracy. Therefore, the technique of choice used most frequently for their quantitative analysis is HPLC-MS/MS. IDs have frequently been detected at concentrations up to the $\mu\text{g L}^{-1}$ range in STP influents (untreated wastewater) in Europe and the United States.

IDs and metabolites have been analyzed by online SPE-LC-ESI-MS/MS following a methodology previously described by Postigo *et al.* [17] for wastewater analysis that can be readily adapted and validated for the analysis of groundwater matrices [59]. IDs in biological matrices are commonly investigated in forensic science, clinical toxicology, and doping control.

6.5 Illicit Drugs in the Environmental Compartments

Compared with PCs, little attention has been devoted to the environmental fate and transport of IDs.

The chemicals associated with clandestine drug laboratories (e.g., drugs, their precursors, by-products, etc.) are often illegally disposed off into the sink, toilet, soil, sewerage system, and public waste management facilities [60, 61]. These chemicals once released may undergo diverse processes such as sorption, degradation, leaching, surface runoff, and so on. Moreover, they become exposed throughout the environmental compartments (i.e., soil, sediments, groundwater, surface water, etc.), and eventually may have potential implications for humans and wildlife. Thus the environmental impact of these potentially toxic chemicals is increasingly being recognized as a critical concern.

Similar to the licit PCs, IDs, may have potent pharmacological and biological activities. Their presence in surface waters even at low environmental concentrations together with the residues of many therapeutic PCs and several other organic compounds may lead to unexpected pharmacological interactions causing toxic effects to aquatic organisms, or may cause a wide variety of environmental and human health problems [19, 62, 63].

The drugs that have been detected in the environmental media are generally those most widely used worldwide, including cannabinoids, amphetamines, opioids, and cocaine. Some related opioid PCs such as codeine and methadone have also been detected in wastewater and surface water of several countries in Europe. The molecules detected generally were the main urinary excretion products, either the unchanged parent drugs or their most abundant metabolites.

Following some studies by Zuccato *et al.* [9] on therapeutic drugs in environmental waters, scientists started to wonder whether IDs, too, could be tracked in rivers and urban sewage. Cocaine was chosen as the first drug to be searched for and measured in environmental water samples. Except for a preliminary study published in 2004 reporting amphetamines in effluents of some STPs in the United States [57], this was the first systematic study exploring IDs in the environment. Cocaine and its major urinary metabolite (benzoylecgonine) were identified in all wastewater samples.

According to Daughton [22], of all the samples analyzed in 2008 by U.S. local and state forensic laboratories, 25 controlled substances composed 90% of all the samples. Of these 25 drugs, the four most frequent were tetrahydrocannabinol (THC), cocaine (benzoylecgonine), methamphetamine, and heroin. Seven were narcotic analgesics (codeine, hydrocodone, oxycodone, methadone, morphine, buprenorphine, and hydromorphone), four were benzodiazepines (alprazolam, clonazepam, diazepam, and lorazepam), and others included MDMA, 3,4-methylenedioxyamphetamine, amphetamine, methylphenidate, phencyclidine, pseudoephedrine, carisoprodol, 1-benzylpiperazine (BZP), and psilocin. In addition to these top 25, other drugs frequently used for non-medical purposes included narcotic analgesics (butorphanol, dihydrocodeine, fentanyl, meperidine, nalbuphine, opium, oxymorphone, pentazocine, propoxyphene, and tramadol) (see Figure 6.8), benzodiazepines (chlordiazepoxide, flunitrazepam,

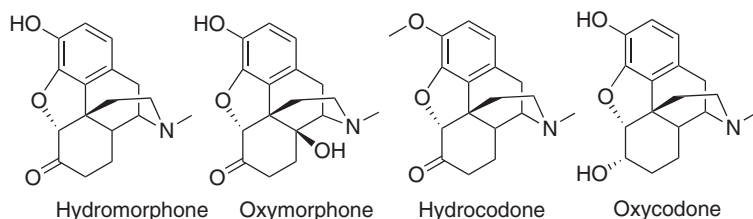


Figure 6.8 Chemical structure of main illicit substances.

midazolam, temazepam, and triazolam), “club” drugs,¹⁰ a number of stimulants (e.g., cathinone, ephedrine, and phentermine), and a number of anabolic steroids (e.g., methandrostenolone, nandrolone, and stanozolol). Many of these latter drugs (not the top 25) have never been routinely targeted for monitoring as environmental contaminants.

6.5.1 Illicit Drugs in Wastewater

After consumption, IDs are excreted as the parent compound and/or metabolites in urine and feces and reach STPs in substantial amounts. Residues of these

Table 6.1 Levels of illicit drugs (ng L⁻¹) in untreated wastewater influents of several European countries.^{a)}

Compound	Spain ^{b)}	Italy ^{c)}	Switzerland ^{c)}	UK ^{g)}	Belgium ^{e)}	Germany ^{f)}	Ireland ^{g)}
Amphetamine	207	17	<LOQ	5236	–	–	–
Methamphetamine	6	13	<LOQ	8 ^{h)}	–	–	–
MDMA	123 ⁱ⁾	8.4	9.7	11 ^{h)}	–	–	–
Cocaine	595 ⁱ⁾	430	215	526	93	–	489
BE	1675 ⁱ⁾	1073	504	1229	629	78	290
nor-BE	–	32	1.8	–	–	–	–
Morphine	71 ⁱ⁾	81	218	620 ^{h)}	–	310	–
6-Acetylmorphine	9.6 ⁱ⁾	14	8.6	–	–	–	–
Codeine	40	54	193	–	–	220	–
EDDP	7.9	20	94	–	–	–	–
Methadone	10.2	11	49	–	–	–	–
THC-COOH	37.8	62	91	159 ^{h)}	–	–	–

a) LOQ limit of quantification; data taken from Ref. [6].

b) Ref. [13].

c) Ref. [14].

d) Ref. [20].

e) Ref. [35].

f) Ref. [29].

g) Ref. [33].

h) Ref. [15].

i) Ref. [17].

10 Ketamine, 1-(3-trifluoromethylphenyl)piperazine (TFMPP), γ -hydroxybutyrate/ γ -butyrolactone (GHB/GBL), 5-methoxy-*N,N*-diisopropyltryptamine (5-MeO-DIPT), and 3,4-methylenedioxy-*N*-ethylamphetamine.

substances have been documented in untreated wastewater of municipal STPs in several countries in Europe (see Table 6.1) [6].

As shown in Table 6.1, untreated wastewaters (influent) of STPs in Spain, Italy, Switzerland, the United Kingdom, Belgium, Germany, and Ireland contain cocaine at concentrations of hundreds of ng L^{-1} , its major metabolite benzoylecgonine at concentrations of $\mu\text{g L}^{-1}$, and lower concentrations of other metabolites such as norbenzoylecgonine, norcocaine, and cocaethylene.

Morphine and 6-acetylmorphine, a specific metabolite of heroin, have also been detected and measured in several STPs throughout Europe. Morphine median concentrations were lower than 100 ng L^{-1} in Italy and Spain, but higher in Switzerland, Germany, and England (approx. 200, 300, and 600 ng L^{-1} , respectively), presumably in relation to higher consumption of therapeutic morphine in these countries [6].

Opioid PCs such as codeine and methadone and its major metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) were also measured in Italy, Spain, Switzerland, and Germany (codeine only) [6].

Other commonly detected drugs were the amphetamines, including amphetamine, methamphetamine and MDMA; their metabolites 3,4-methylenedioxy-*N*-ethylamphetamine and 3,4-methylenedioxymphetamine; and the active principle in cannabis, THC, and its metabolites THC-COOH and OH-THC. Ephedrine and trace amounts of ketamine and lysergic acid diethylamide have been measured in Spain [6]. Up to 300 ng kg^{-1} of amphetamine was detected in sewage sludge from an STP in Austria [11].

The majority of the studies deals with the occurrence of IDs in urban wastewater [37, 64, 65] confirming that treatments at the WWTPs are unable to eliminate these pollutants.

Similarly to pharmaceuticals, IDs are often only partially removed by STPs and therefore persist in the effluents (see Table 6.2). Concentrations in effluents are normally lower than those in influents, the differences between substances reflecting their removal rates in STPs. The removal rates of some compounds are reported in the recent literature. For instance, removal of amphetamine and methamphetamine was almost complete (85–99% and 60–98%), and their concentrations in effluents were in the low ng L^{-1} range, whereas the removal rate of MDMA was approximately 50% (44–57%) and its concentrations in treated water were still in tenths of ng L^{-1} . Cocaine, benzoylecgonine and morphine were extensively removed in STPs (removal rates of 72–100%, 83–100%, and 72–98%) and their concentrations in effluents were approximately 10% of those in influents. By contrast, methadone and its metabolite EDDP proves resistant to degradation in STPs, with low removal rate (9–22% and 8–27%), and their concentrations in effluents are still close to those in influents. Codeine and THC-COOH were variably removed in different STPs (removal rate ranges were 12–100% and 11–99%, respectively), resulting in variable levels in effluents.

Despite the fact that IDs are generally well removed in STPs (removal higher than 60%), several substances were still detected at concentrations of up to the hundreds of ng L^{-1} in STP effluents.

Also, several substances were found at higher concentrations in effluents than in influents [28]. These compounds were those excreted mainly as

Table 6.2 Levels of illicit drugs (ng L⁻¹) in treated wastewater effluents of several European countries.^{a)}

Compound	Spain ^{b)}	Italy ^{d)}	Switzerland ^{d)}	UK ^{e)}	Germany ^{f)}	Ireland ^{g)}
Amphetamine	28	2.6	<LOQ	127	–	–
Methamphetamine	6	2.3	<LOQ	–	–	–
MDMA	56	4.7	4.2	–	–	–
Cocaine	10	<LOQ	11.3	149	–	94
Benzoyllecgonine	90	0.57	88	1597	49	26.5
<i>nor</i> -Benzoyllecgonine	–	1.8	6.5	–	–	–
<i>nor</i> -Cocaine	–	<LOQ	0.8	–	–	–
Cocaethylene	–	<LOQ	<LOQ	–	–	–
Morphine	10.4 ^{c)}	1.5	59	–	40	226
Codeine	35.1 ^{c)}	<LOQ	144	–	85	–
EDDP	7.2 ^{c)}	22.6	73	–	–	58
Methadone	9.4 ^{c)}	9.1	36	–	–	–
THC-COOH	33.7 ^{c)}	0.6	7	–	–	–

a) LOQ limit of quantification; data taken from Ref. [6].

b) Ref. [16].

c) Ref. [28].

d) Ref. [14].

e) Ref. [34].

f) Ref. [29].

g) Ref. [33].

glucuronide metabolites, which can be deconjugated by the β -glucuronidase enzymes of the fecal bacteria in wastewater. For example, the transformation of morphine-3 β -D-glucuronide to free morphine was also observed during a 3-day stability test in wastewater [14]. The amounts of IDs detected in wastewater could roughly reflect the amounts consumed [9].

6.5.2 Illicit Drugs in Surface Water

Treated wastewater is generally discharged into surface waters (rivers, lakes, sea) or undergoes further treatment to produce drinking water. Substantial amounts of IDs therefore directly enter surface waters or DWTPs. These substances are still detectable in rivers and lakes up to tenths of ng L⁻¹ in several countries [66].

Cocaine and its metabolites (benzoyllecgonine and *nor*-benzoyllecgonine), codeine, and methadone and its metabolite EDDP were encountered in 100% of surface water samples collected in the Po river. Results from Zuccato *et al.* [9] reported average concentrations in the Po river of cocaine and benzoyllecgonine of 0.001 and 25 ng L⁻¹, respectively.

Drugs of abuse have been measured in rivers in Italy (Po, Olona, Lambro, and Arno), Spain (Llobregat), the United Kingdom (Thames, Taff, and Ely), Belgium (3 rivers), Germany (11 rivers) and Ireland (2 rivers) and in lakes in Italy (Maggiore, Como, and Lugano). The findings are summarized in Table 6.3. Median levels

Table 6.3 Levels of illicit drugs (ng L⁻¹) in surface water of several European countries.^{a)}

Compound	Spain ^{b)}	Italy ^{c)}	UK	Belgium ^{d)}	Germany ^{e)}	Ireland ^{f)}
Amphetamine	9	<LOQ	3.5 ^{g)}	–	–	–
Methamphetamine	1	1	–	–	–	–
MDMA	3	1.1	4	–	–	–
Cocaine	10	1	5 ^{c)}	13	–	29
Benzoylecgonine	50	14	23 ^{g)}	53	3	<LOQ
<i>nor</i> -Benzoylecgonine	–	1.2	–	–	–	–
<i>nor</i> -Cocaine	–	0.3	–	–	–	–
Cocaethylene	–	0.1	–	–	–	–
Morphine	5.2	3.5	8	–	10	<LOQ
Codeine	23	7	–	–	38	–
EDDP	12	5	–	–	–	<LOQ
Methadone	5.4	2.5	–	–	–	–
THC-COOH	24	0.7	1	–	–	–

a) LOQ limit of quantification; data taken from Ref. [6].

b) Reference [13].

c) Reference [15].

d) Reference [35].

e) Reference [29].

f) Reference [33].

g) Reference [20].

were up to tenths of ng L⁻¹ for cocaine and benzoylecgonine, a few ng L⁻¹ for amphetamines, morphine, codeine, methadone, and EDDP and trace amounts or below the LOQ for the other substances and metabolites [6].

6.5.3 Illicit Drugs in Seawater

Jiang *et al.* [67] showed concentrations of several licit and illicit drugs in seawater (see Table 6.4).

6.5.4 Illicit Drugs in Drinking Water

IDs were also evaluated in raw waters used for drinking-water production and in finished drinking water in a Spanish DWTP. Levels in the river basin supplying raw water to this DWTP were also monitored. In surface waters, cocaine, benzoylecgonine, amphetamine, methamphetamine, MDMA, and 3,4-Methylenedioxymphetamine were detected at mean concentrations from 4 to 350 ng L⁻¹ [13].

Trace amounts of benzoylecgonine, methadone and its main metabolite, EDDP, were still present in finished drinking water in a Spanish DWTP [66].

The elimination of these compounds during drinking-water treatment was investigated. ATs (except MDMA) were completely removed during pre-chlorination, flocculation, and sand-filtration steps. Subsequent granulated activated carbon filtration removed cocaine (100%), MDMA (88%) and benzoylecgonine (72%), and post-chlorination removed 90% benzoylecgonine, which was still detectable in drinking water despite the high percentage of

Table 6.4 Concentration (ng L⁻¹) of selected emerging organic contaminants in southwestern Taiwan.^{a), b)}

Compound	Min	Max	Mean
Acetaminophen	2.6	16.7	8.44
Ibuprofen	n.d.	12.1	2.61
Ketoprofen	n.d.	23.3	8.69
Codeine	n.d.	63.6	22.15
Ampicillin	n.d.	88.7	6.88
Erythromycin	n.d.	26.6	2.83
Cefalexin	n.d.	9.19	2.03
Caffeine	1.24	16.92	4.28
Carbamazepine	n.d.	3.83	0.25
Gemfibrozil	n.d.	3.67	0.75
Ketamine	n.d.	21.1	3.69
Pseudoephedrine	0.71	2.65	1.40
MDMA	n.d.	4.82	0.51

a) Data taken from Ref. [67].

b) n.d. = not detected.

removal. This metabolite was found in 22 of 24 drinking water samples at a mean concentration of 45 ng L⁻¹ and a maximum of 130 ng L⁻¹ [13].

6.5.5 Illicit Drugs in Soil

Most IDs have never been monitored in biosolids or sediments. Domènech *et al.* [68] used fugacity modeling to predict the fate of cocaine and BZE. The microbial degradation of methamphetamine has been reported by Janusz *et al.* [60]. Wick *et al.* [69] examined biological removal in activated sludge and found rapid removal for morphine, codeine, dihydrocodeine, oxycodone, and methadone.

The sorption of IDs to sediments was also reported [69, 70]. Wick *et al.* [69] and Barron *et al.* [71] acquired low distribution coefficients (K_d) for amphetamine, cocaine, cocaethylene, BZE, MDMA, morphine, codeine, dihydrocodeine, methadone, and tramadol, showing that removal via sorption to sewage sludge is possibly negligible.

The data on toxicological studies suggest that the disruption of normal microbial function in the selected soils is likely to occur only at relatively high concentrations of the test compounds. This was observed for only six compounds, where dehydrogenase activity was reduced. Since dehydrogenase activity is an indicator of active microbial biomass generally used to study the effects of pollutants on microorganisms in soil, this observed effect is worth further consideration [47].

The degradation study [47] revealed that MDMA, pseudoephedrine, and 1-(1,4-cyclohexadienyl)-2-methylaminopropane were less persistent in all three test soils than were methamphetamine, *N*-formylmethamphetamine, and 1-benzyl-3-methylnaphthalene, over a one-year incubation period. In general, resistance to degradation in non-sterile soils was recorded in the

following in descending order: 1-benzyl-3-methylnaphthalene > methamphetamine > *N*-formylmethamphetamine > MDMA > pseudoephedrine > 1-(1,4-cyclohexadienyl)-2-methylaminopropane. In sterile soils, methamphetamine and 1-benzyl-3-methylnaphthalene showed no measurable changes in concentration level over a one-year incubation period. Among the target compounds, 1-(1,4-cyclohexadienyl)-2-methylaminopropane was found to be most susceptible to degradation. It transformed into methamphetamine mostly within a few weeks in all the test soils.

6.5.6 Illicit Drugs in Ambient Air

Unlike the vast majority of PCs, certain IDs have the potential to escape to the ambient air, primarily because of the release of vapors and particulates from smoking and inhalation and from the generation of dust. Perhaps, the first data on an ID in the environment were from the 1998 report of cocaine associated with particulates in ambient outdoor air in Los Angeles [72]. Since then, studies have actively targeted a limited array of IDs in ambient air in several locales, primarily cities in Italy and Spain, and also in Serbia, Portugal, Algeria, Chile, and Brazil. An overview of this topic is provided by Postigo *et al.* [45].

The major studies include Balducci *et al.* [73], Cecinato and Balducci [10], Cecinato *et al.* [74], and Viana *et al.* [75]; another base of knowledge regarding analytical methodologies exists in the forensics literature, such as the work of Lai *et al.* [76]. Residues are usually associated with airborne particulates. Concentrations of cocaine generally are in the low pg m⁻³ level but can range up to low ng m⁻³ levels. Levels within a geographic region can vary by two or more orders of magnitude and are sensitive to weather conditions and time of year (with higher concentrations in winter) [74]. These highest levels are roughly three orders of magnitude lower than commonly found for caffeine or nicotine.

The objective of air monitoring for IDs is more in line with forensics (as a tool in detecting trends in drug use) than with concerns regarding public health impacts from chronic pulmonary exposure to trace ambient levels.

Traces of IDs were also detected in airborne particulates in several cities across the world, indicating the possible distribution of these substances in the air compartment, despite their polarity and high water solubility [66].

6.5.7 Illicit Drugs on Currency Notes

Residues of IDs have been known since the 1980s to occur on banknotes [7], primarily as a result of dermal transfer from drug users and transfer from contact with bulk drugs themselves. Highly contaminated banknotes can, in turn, cross-contaminate pristine banknotes in their proximity. Most research has been focused on cocaine, because of its propensity to become entrapped in banknote fibers and because of the use of bank notes for insufflation.

Cocaine amounts exceeding 1 mg per banknote have been reported [77], more than 1% of a typical dose. The contamination is so pervasive that large numbers of banknotes are forced to be removed from general circulation each year. Bones *et al.* [78] pushed the limit of detection for cocaine into the range of 1 pg per banknote. In addition to cocaine, other drugs studied on banknotes

include 6-AM, diacetylmorphine (DAM), Δ^9 -tetrahydrocannabinol, cannabinol, cannabidiol, MDMA, methamphetamine, amphetamine, phencyclidine, and codeine.

Although the occurrence of IDs on money in general circulation possibly serves as a minor source of exposure for the public, via dermal transfer and pulmonary exposure, no work has been done on these routes. Interest has been spurred instead by forensic experts – primarily with the potential to distinguish “drug money” from “innocent” money. The forensics aspects of drug-contaminated money have been advanced largely by MS. Overviews are available from Sleeman *et al.* [79] and Armenta and De la Guardia [80]. Numerous works have been published, a few of which are by Bones *et al.* [78], Carter *et al.* [81], Ebejer *et al.* [82], Jenkins [83], Lavinset *et al.* [84], Luzardo *et al.* [85], Sleeman *et al.* [86], and Zuo *et al.* [87].

6.6 Estimation of Drug Consumption in Communities (Sewage-Based Epidemiology)

ID use causes substantial global health problems and social harm both directly and indirectly (e.g., overdose, blood borne viruses, violence) [88]. Accurate and reliable data on ID consumption is needed to plan and assess the impact of interventions aimed at reducing drug use. Traditional monitoring methods that rely on self-report (e.g., population surveys) may underestimate drug use because it is an illegal, stigmatized activity. Additionally, these methods are expensive, time-consuming, and incomplete [89].

The prevalence of drug use is currently estimated by subjective methods such as population surveys. As recommended by the United Nations Commission of Narcotic Drugs,¹¹ new approaches are required to provide more realistic and comparable estimates of ID consumption in different communities. Data on drug monitoring at STPs was used by Zuccato *et al.* [9] to assess collective drug consumption for cocaine. Consequently, sophisticated analytical methods for the simultaneous measurement of a cocktail of IDs have been set up [14, 17, 18, 28, 29, 33]–[38, 42, 56]–[58, 90] and reviewed by Castiglioni *et al.* [91] and Postigo *et al.* [92]. Therefore, scientists have developed the following innovative, complementary method of estimating community drug use by quantifying drug residues in sewage, which contains urine from the entire population:

- 1) Collect a sewage sample.
- 2) Measure concentrations of drug residues in the samples.
- 3) Calculate sewage drug loads (concentrations multiplied by sewage volume).
- 4) Correct for human metabolism (excretion rate).
- 5) Normalize total loads with population size.

11 UNODC (United Nations Office of Drugs and Crime). 2007 Commission on Narcotic Drugs, draft resolution E/CN.7/2007/L.16/Rev.1. See http://www.unodc.org/unodc/cnd_session_50_drafts.html.

To ensure reliable results, sewage-based epidemiology requires significant expertise from numerous disciplines:

- Environmental engineers design sample collection to guarantee that sewage samples are representative of the community's excreted urine.
- Analytical chemists develop methods to accurately quantify drug residues.
- Environmental chemists investigate transformation in sewers.
- Pharmacologists define the identity and amounts of excreted drug residues to estimate total consumption.
- Epidemiologists identify how this information can complement traditional methods to estimate prevalence of substance use.
- Social scientists assess ethical aspects of sewage analysis.

Flushed via toilets, excreted drug residues in sewers can be subject to high short-term dynamics and diurnal variations. Both need to be considered in order to obtain a representative sample [93]. A thorough experimental design assesses the definition of catchment area, hydraulic properties, and the sampling setup, which are elicited from utilities with specifically tailored questionnaires [94]. Typically, a sample of 500 mL of raw sewage, filtered and stabilized until analysis, is sufficient. Analyte concentrations are at the low ng L⁻¹ level, which necessitates sample cleanup, pre-concentration and subsequent chemical analysis via highly specific and sensitive techniques, normally based on LC-MS/MS [95]. The analyte of choice in sewage-based epidemiology is generally the primary urinary metabolite of the drug of interest.

To facilitate comparison among cities and to estimate consumption, sewage drug loads are normalized by the number of people and corrected for excretion rates of the metabolite and drug purity. Excretion rates are available from clinical studies, and drug purity is determined through analysis of drugs from local seizures or test purchases. However, it must be noted that, a reliable estimate of the population contributing to the sewage is difficult: census may be outdated or may not coincide with the geographical boundary of a sewer catchment, and accounting for commuters and tourists is challenging. One solution is to measure simultaneously specific compounds in the sewage samples to estimate population size.

Cocaine and benzoylecgonine were identified by MS in untreated waste-water samples from four medium-sized Italian cities and from the Po river. Using the levels of benzoylecgonine to estimate the corresponding loads of cocaine, it was found that local drug consumption was considerably higher than current estimates.

This approach was subsequently extended to other IDs including amphetamines, opioids, and cannabis. By monitoring selected drug residues entering the municipal STPs of Milan, London, and Lugano, this study provided an objective, quantitative, real-time profile of ID consumption in these cities [15]. This quantitative approach was therefore proposed as an additional tool to estimate drug abuse better in real time [9, 96].

Daily loads of the drug residues were measured in the rivers Po, Arno, Lambro, and Olona [6, 19]. The Po carried up to 390 g of benzoylecgonine daily, equivalent to approx. 1 kg of cocaine, 60 g of pure cocaine, 30 g of amphetamines, 38 g of the

cannabis metabolite THC-COOH, and 196 g of methadone and its metabolite EDDP. Loads were lower in the Arno, Lambro and Olona.

The European Monitoring Centre of Drugs and Drug Abuse (EMCDDA) reports a drug use prevalence in Italy in 2012 of 3.5%, similar to Portugal, Austria, Slovakia and Slovenia. This data include adults aged between 15 and 64 that have been consuming cannabis, cocaine, heroin, amphetamines, MDMA, and hallucinogens [97].

In 2011, van Nuijs *et al.* [95] made a review aimed at critically evaluating the published literature and identifying research gaps of sewage epidemiology using back-calculations to transform measured concentrations in wastewater (in ng L^{-1}) for the four groups of IDs into an amount of used ID (in g d^{-1} per 1000 inhabitants or doses d^{-1} per 1000 inhabitants). The results derived from wastewater analysis in general showed good agreement with existing prevalence data.¹² and demonstrated the potential of sewage epidemiology

In 2012, Thomas *et al.* [98] published a study comparing ID (cocaine, amphetamine, MDMA, methamphetamine, and cannabis) use in 19 European cities through sewage analysis. In this study, raw sewage was collected from the inlet of 21 STPs spread over 11 European countries, representing 19 cities, and servicing a combined population of approximately 15 million inhabitants. Samples were collected from each location over seven consecutive days and it was observed that cocaine use was higher in Western and Central Europe and lower in Northern and Eastern Europe. The extrapolated total daily use of cocaine in Europe during the study period was equivalent to 356 kg d^{-1} . High per capita MDMA loads were observed in Dutch cities, as well as in Antwerp and London. In general, cocaine and MDMA loads were significantly elevated during the weekend compared to weekdays. Per-capita loads of methamphetamine were highest in Helsinki and Turku, Oslo and Budweis, while the per capita loads of cannabis were similar throughout Europe [98].

The quantitative analysis of sewage for the estimation of ID use is complementary to existing epidemiologically based approaches and can provide additional, evidence-based information.

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¹² Percentage of a population that uses IDs at a given time.

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7

Pesticides as Pollutants

7.1 Introduction

The term “-cide” has its origin in Latin, meaning “to kill.” The EPA defines pesticides as any substance or a mixture of substances intended for preventing, destroying, repelling, or mitigating any pest.¹

Many types of pesticides are effective against specific pests such as insects, parasites, fungi, weeds, rodents, and so on. Pesticides are used in agriculture related to crop growth, storage, and transport; in food marketing; in wood and wood products in industries; in livestock for the control of insects, arachnids, and other pests; in gardening; and in household maintenance. These chemicals play a key economic role and serve human health by killing vectors of many diseases. Pesticides in agriculture are rarely used in pure or technical-grade form. The active component that acts against pests/plant diseases is termed “active substance” and, mixed with other components, constitutes the pesticide formulation. These ingredients are often called as “inert,” although the term is potentially misleading, and they serve a variety of functions, for example, to stabilize active components or to provide a better application to improve absorption by plants. Most are synthetic organic compounds but in recent years a new group of pesticides have become an effective tool for pest control, the so-called biopesticides. The EU considers biopesticides as “a form of pesticide based on microorganisms or natural products” and the EPA defined biopesticides as naturally occurring substances that control pests (biochemical pesticides), microorganisms that control pests (microbial pesticides), and pesticidal substances produced by plants containing added genetic material. The International Union of Pure and Applied Chemistry (IUPAC) has adopted the same criteria for biopesticides as EPA.²

The EU has compiled a database for active substances according to Regulation (EC) No 1107/2009 [1],³ which is periodically updated. Concurrently, EPA has developed its own database for pesticides with similar information.⁴

1 <http://www.epa.gov/minimum-risk-pesticides/what-pesticide>.

2 http://agrochemicals.iupac.org/index.php?option=com_sobi2&sobi2Task=sobi2Details&catid=3&sobi2Id=7.

3 <http://ec.europa.eu/food/plant/pesticides/eu-pesticides-database>.

4 Office of Pesticide Programs. Pesticide Chemical Search: Conventional, antimicrobial and biopesticide active ingredients. EPA, 2017. <https://iaspub.epa.gov/apex/pesticides/f?p=CHEMICALSEARCH>.

About 2.4 million t of pesticides were used worldwide in 2007 [2]. Herbicides accounted for the largest portion of total use, followed by other pesticides, insecticides, and fungicides. In 2007, the United States accounted for 22% of the total world pesticide amount used [3]. According to Eurostat,⁵ the use of pesticides in Italy, in 2006, reached 81,500 t, more than any other European country. From 2002 to 2007, the use of conventional pesticides decreased approximately 3%, 11% from 1997 to 2007.⁶

The top 10 pesticides used worldwide in the agricultural market are herbicides glyphosate, atrazine, metolachlor-S, acetochlor, 2,4-D, and pendimethalin, and the fumigants metam-sodium, dichloropropene, methyl bromide, and chloropicrin. According to the food and drugs administration (FDA) of the United Nations program on the prevention and disposal of obsolete pesticides, “half a million t of obsolete pesticides are scattered throughout the developing world. These toxic chemicals, often stored outdoors in leaking containers, are seeping into the soil and water.”

7.2 Classification of Pesticides

There are more than 20,000 pesticide compounds with a wide range of applications, uses, and chemical structures, and also, many of them show multiuse role. Table 7.1 lists typical uses of pesticides in several fields.

Table 7.1 Classification of pesticides according to their use.^{a)}

Activity	Use
Agriculture	Control of multiple crop pest
Public health	Control of disease vectors (i.e., dengue, leishmaniasis, typhus, etc.); Control of pests (rodents); eradication of illegal plantations that produce illicit drugs
Livestock and domestic care animals	Disinfection of animals
Treatment of structure	Treatment of buildings (private or public)
Maintenance of green areas	Treatment of parks, gardens, etc.
Maintenance of water reserves	Treatment of large water reserves (natural or artificial)
Industry	Manufacture of refrigerators, electrical equipment, paints, packaging in food industry, etc.
Home	Incorporated in products such as cosmetics, soaps, insect repellents, etc.

a) Data taken from <http://edis.ifas.ufl.edu/pdffiles/PI/PI08300.pdf>.

5 European Commission Statistical Office-Eurostat (2012) “Agri-environmental indicator – consumption of pesticides.” http://ec.europa.eu/eurostat/statistics-explained/index.php/Agri-environmental_indicator_-_consumption_of_pesticides.

6 U.S. Environmental Protection Agency (EPA), About Pesticides (2014). <http://www.epa.gov/pesticides/about/index.htm>.

Pesticides can be classified according to three main criteria:

- Use and activity.
- Toxicity.
- Chemical structure.

7.2.1 Classification of Pesticides by Activity

Table 7.2 shows a useful way to describe pesticides classified according to their primary target pest and action.

7.2.2 Classification of Pesticides by Toxicity

The WHO has recommended a classification of pesticides according to hazard more than active component or use [4]. This classification is based on dermal

Table 7.2 Pesticides classified according to target pests and action.^{a)}

Pesticide class	Primary target/action	Examples
Acaricide	Mites	Aldicarb, bifenazate
Algaecide	Algae	Copper sulfate
Attractant	Wide range of pests	Pheromones
Avicide	Birds	Avitrol (aminopyridine)
Bactericide	Bacteria	Copper complexes, streptomycin
Bait	Wide range of organisms	Anticoagulants
Biopesticide	Wide range of organisms	<i>Bacillus thuringiensis</i>
Defoliant	Kills plant foliage	Tribufos
Desiccant	Removes water	Boric acid
Fumigant	Wide range of organisms	Aluminium phosphide
Fungicide	Fungi	Azoxystrobin, chlorothalonil
Herbicide	Weeds	Atrazine, glyphosate, 2,4-D
Insect growth regulator	Insects	Diflubenzuron
Insecticide	Insects	Aldicarb, carbaryl, imidacloprid
Molluscicides	Snails, slugs	Metaldehyde
Nematicide	Nematodes	Aldicarb, fenamiphos
Piscicide	Fish	Rotenone
Plant growth regulator	Regulates plant growth	Gibberellic acid, 2,4-D
Predacide	Mammal predators	Strychnine
Repellent	Vertebrates and invertebrates	<i>N,N</i> -Dimethyl- <i>m</i> -toluamide (DEET), methiocarb
Rodenticide	Rodents	Warfarin
Silvicide	Trees	Tebuthiuron
Termiticide	Kills termites	Fipronil

a) Data taken from <http://edis.ifas.ufl.edu/pdffiles/PI/PI08300.pdf>.

Table 7.3 WHO classification of pesticides by hazard.

WHO class	Degree of hazard	Rat LD ₅₀ (mg kg ⁻¹ bw)	
		Oral	Dermal
Ia	Extremely	<5	<50
Ib	Highly	5–50	50–200
II	Moderately	50–2000	200–2000
III	Slightly	Over 2000	Over 2000
U	Unlikely to present acute hazard	5000 or higher	

and oral toxicity parameter value, LD₅₀, on rats by standard procedures used in toxicology. The dermal LD₅₀ value is a more restrictive parameter than the oral LD₅₀. Pesticides are divided into five groups, and Table 7.3 summarizes the WHO classification.

In case of formulations and mixtures, the calculation of LD₅₀ is as follows:

$$\frac{\text{LD}_{50} \text{ active ingredient}}{\% \text{ of active ingredient in formulation}} \times 100 \quad (7.1)$$

7.2.3 Classification of Pesticides by Chemical Structure

A wide range of functional groups and structures can be found in all the pesticides described, most of them organic compounds. According to their chemical structure, pesticides can be classified into different families, the two major groups being organic and inorganic compounds.

For many years, highly toxic inorganic pesticides have been used despite their neurotoxicity. Examples of these types of compounds are arsenic, copper, lead, mercury, or tin derivatives, or less toxic ones such as borates, silicates, and sulfur derivatives. Current inorganic pesticides are relatively low in toxicity and have low environmental impact. For example, borate insecticides, such as bora care and timbor, obtained from minerals.

In the case of organic pesticides, it is difficult to develop an exhaustive classification of pesticides according to their chemical structure.

7.3 Organic Pesticides

Despite their chemical diversity, several groups can be distinguished. The top 10 pesticide classes, based on amounts used to total global pesticides consumption in decreasing order, are [5]: Dithiocarbamates, organophosphates, phenoxy alkanolic acids, amides, bipyridyls, triazines, diazoles and triazoles, carbamates, urea derivatives, and pyrethroids.

7.3.1 Organochlorine Pesticides

Organochlorine pesticides, organic compounds with chlorine atoms, are the first synthetic organic pesticides to be used in agriculture and in public health for the

control of a wide range of pests. Organochlorines present a long-term residual effect in the environment because of their persistence and bioaccumulation properties since they are resistant to most microbial and chemical degradations and may be incorporated into the food chain.

Organochlorine insecticides act as nervous-system disruptors leading to convulsions and paralysis of the insect and its eventual death. For other living beings the effects of organochlorine pesticides depend on the specific substance and the level and timing of exposure as well as the individual response of each species.

Many of the most used organochlorine pesticides over several decades from the 1940s are included in the list of the so-called “dirty dozen,” a group of compounds that present a global concern because of their environmental impact. In 2001, a treaty known as the Stockholm Convention were signed by around 90 countries to reduce or eliminate the production, use, and/or release of these 12 key POPs (see Figure 7.1 and Table 7.4).

DDT is a clear example of the massive use of such compounds. It was the first of the organochlorine insecticides that were used from the 1940s. From the beginning, it showed great efficiency against malaria, typhus, and other human diseases transmitted by insects and also for insect control in agriculture, livestock, institutions, homes, and gardens. DDT's quick success as a pesticide all over the world, however, raised two problems associated with its massive use: the development of resistance by many insect pest species, and the evidence of environmental and toxicological effects. The publication of Rachel Carson's book “Silent Spring” in 1962 stirred public concern over the dangers of improper use of not only of

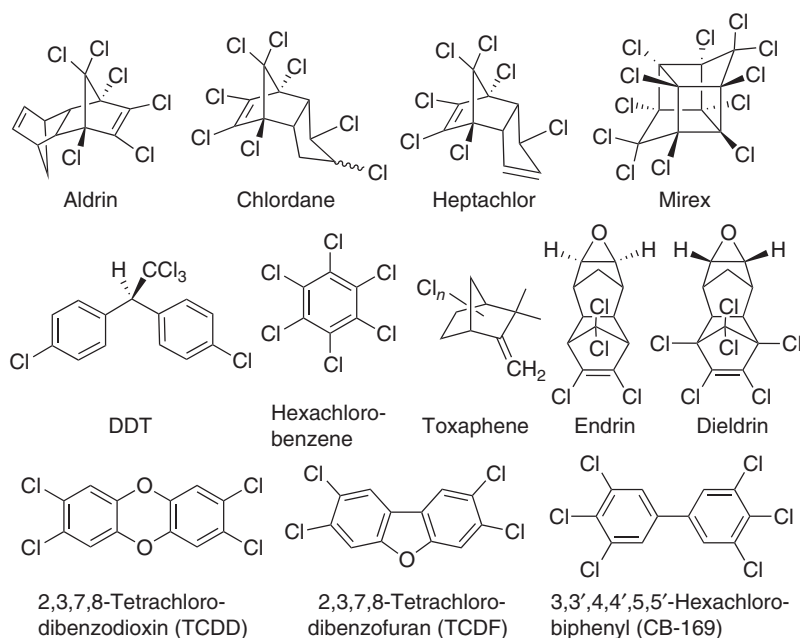


Figure 7.1 Chemical structure of the “dirty dozen” POPs.

Table 7.4 List of the “dirty dozen” POP compounds and use/source.

POP	Global historical use/source
Aldrin and dieldrin	Insecticides used for pest on corn and cotton, and termite control
Chlordane	Insecticide used on vegetables, small grains, potatoes, sugar cane, sugar beets, fruits, nuts, citrus, and cotton. Used on home lawn and garden pests. Also used extensively to control termites
DDT	Insecticide used on agricultural crops, primarily cotton, and insects that carry diseases such as malaria and typhus
Endrin	Insecticide used on crops such as cotton and grains, also used to control rodents
Mirex	Insecticide used to combat fire ants, termites, and mealybugs. Also used as a fire retardant in plastics, rubber, and electrical products
Heptachlor	Insecticide used primarily against soil insects and termites. Also used against some crop pests and to combat malaria
Hexachlorobenzene	Fungicide used for seed treatment. Also an industrial chemical used in the manufacture of fireworks, ammunition, synthetic rubber, and other substances. Also unintentionally produced during combustion and the manufacture of certain chemicals. Also an impurity in certain pesticides
PCBs	Used for a variety of industrial processes and purposes, including in electrical transformers and capacitors, as heat exchange fluids, as paint additives, in carbonless copy paper, and in plastics. Also unintentionally produced during combustion
Toxaphene	Insecticide used to control pests on crops and livestock, and to kill unwanted fish in lakes
Dioxins and furans	Unintentionally produced during most forms of combustion, including burning of municipal and medical wastes, backyard burning of trash, and industrial processes. Also can be found as trace contaminants in certain herbicides, wood preservatives, and in PCB mixtures

pesticides, but also other chemical substances and the need for better controls and more accurate regulations [6].

7.3.2 Organophosphorus Pesticides

Organophosphorus compounds are derived from phosphoric acid and although they were developed in the 1940s for pesticide use, they have been used increasingly since the 1970s, replacing DDT. Organophosphorus pesticides show several advantages over other pesticides, as they are generally short-lived in the environment, lasting only from days to months instead of years before degrading, and, generally, chemical breakdown is accelerated when temperature and/or pH becomes higher. Structures of several families of this group of

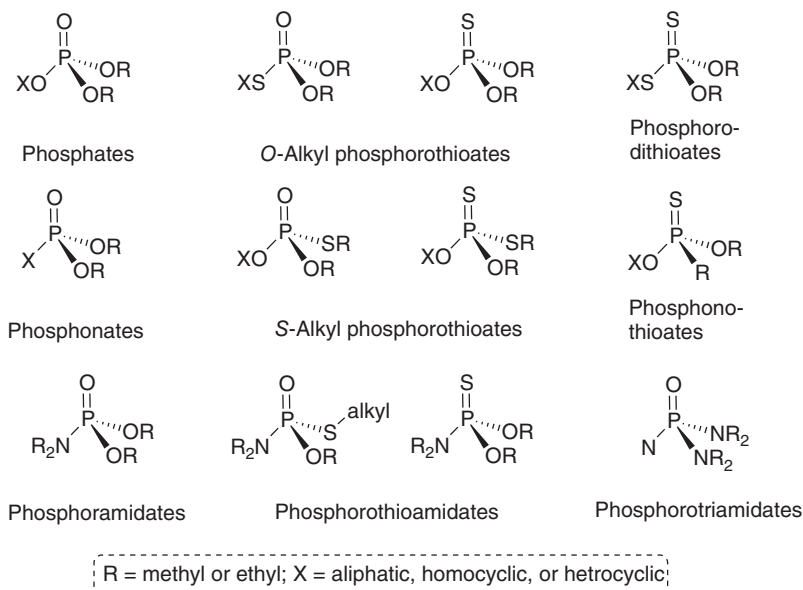


Figure 7.2 General structure of several families of organophosphorus pesticides.

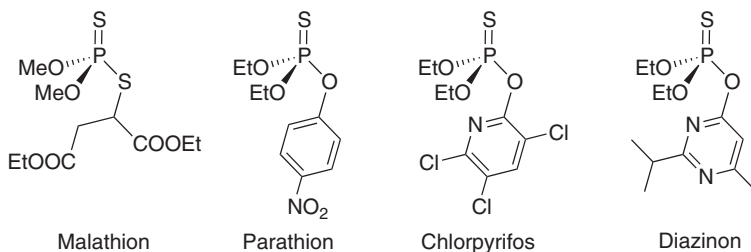


Figure 7.3 Structure of the most common organophosphorus pesticides.

pesticides are summarized in Figure 7.2. The toxicity of organophosphorus pesticides is apparent in the disruption of the nervous system of an invertebrate or a vertebrate and is a result of the inhibition of cholinesterase enzymes in organisms as well as in the targeted pests. More common examples are shown in Figure 7.3

7.3.3 Carbamates

Carbamates are a group of pesticides derived from carbamic acid, and are widely used in agriculture as insecticides, nematicides, fungicides, herbicides, or sprout inhibitors, and as biocides for industrial applications, and in household products. They act similarly to organophosphates in their ability to inhibit acetylcholinesterase and other esterases. They are more degradable than organophosphates, yielding lower dermal toxicities. More common examples are shown in Figure 7.4

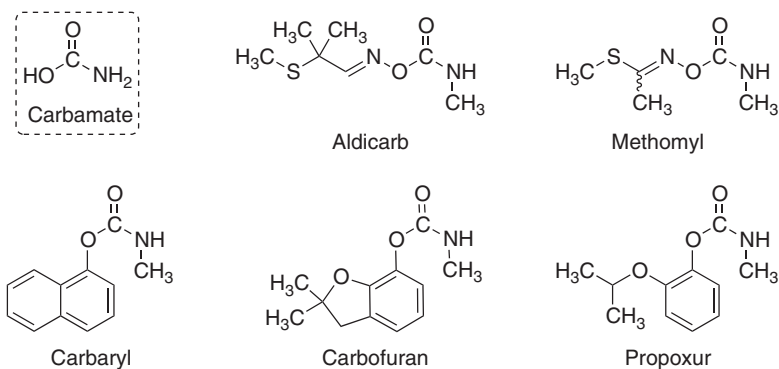


Figure 7.4 Chemical structure of carbamate and common carbamate pesticides.

7.3.4 Thiocarbamates

Thiocarbamates are a group of organosulfur compounds used extensively in agriculture as insecticides, herbicides, and fungicides, and as biocides for industrial applications, as well as in household products. Some of them are used for vector control in public health [7]. They are divided into two classes: monothiocarbamates and dithiocarbamates (see Figure 7.5). Some representative commercial compounds are shown in Figure 7.6.

Thiocarbamates are volatile compounds, and therefore, evaporate from the soil. Dithiocarbamates with hydrophilic groups are able to form water-soluble, heavy-metal complexes, while some of the dithiocarbamate metal complexes

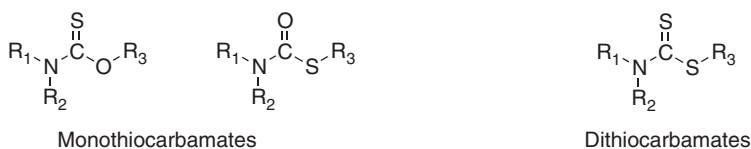


Figure 7.5 Chemical structure of the two classes of thiocarbamates.

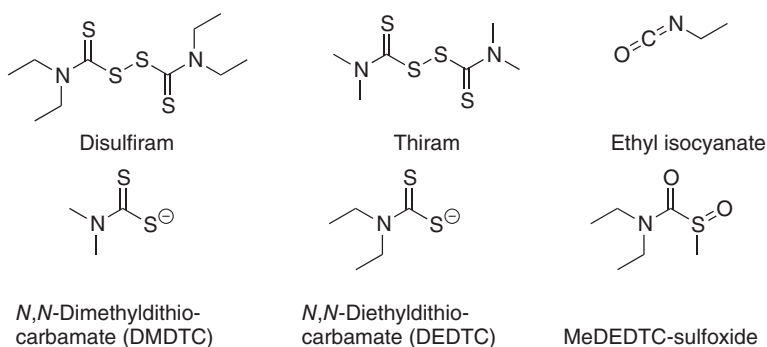


Figure 7.6 Chemical structure of some commercial thiocarbamates.

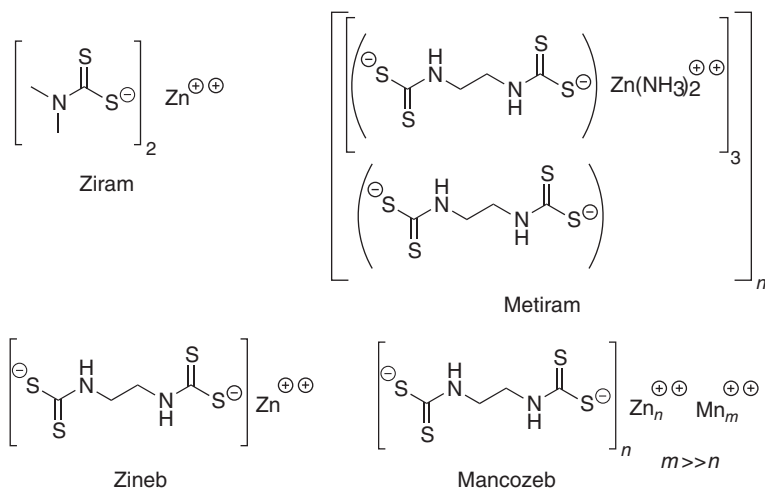


Figure 7.7 Chemical structure of some dithiocarbamate fungicides.

used as fungicides are insoluble in water but soluble in non-polar solvents (see Figure 7.7).

7.3.5 Pyrethrins and Pyrethroids

Pyrethrum is the common name for the *Chrysanthemum cinerariifolium* species formerly called Pyrethrum which has an extract with insecticide properties formed by a mixture of six compounds (pyrethrins), and is used against mosquitoes, fleas, flies, moths, ants, and many other pests. Pyrethroids are synthetic insecticides derived structurally from the naturally occurring pyrethrins. Both, natural and synthetic pyrethrins cause paralysis in targeted insect pests, eventually resulting in death. Two moieties can be distinguished within the pyrethrin structure: acid moiety, derived from chrysanthemic acid, and the alcohol moiety (see Figure 7.8).

From natural pyrethrins, a first generation of synthetic compounds have been prepared as allethrin, and resmethrin, with the acid moiety based on the chrysanthemic acid derivative present in pyrethrin I. This acid has a cyclopropane ring, which is not present in more recent synthetic pyrethroids. A second generation of synthetic pyrethroids can be classified into two groups: Type I, without cyano groups and Type II, containing a cyano group (see Figure 7.9). The introduction of cyano group at the C_α of the 3-phenoxybenzyl-alcohol moiety improves the major breakthrough.

7.3.6 Phenoxy Carboxylic Acids

Phenoxy derivatives are used mainly as herbicides in both crop and non-crop areas for control of most annual and perennial broadleaf weeds. Some commonly used compounds include 2,4-D, MCPA, dichlorprop (2,4-DP), and 2,4-DB (butoxone or butyrac) (see Figure 7.10). These are plant growth regulators and affect the actively growing tissue of the plant. Most of them are derivative esters

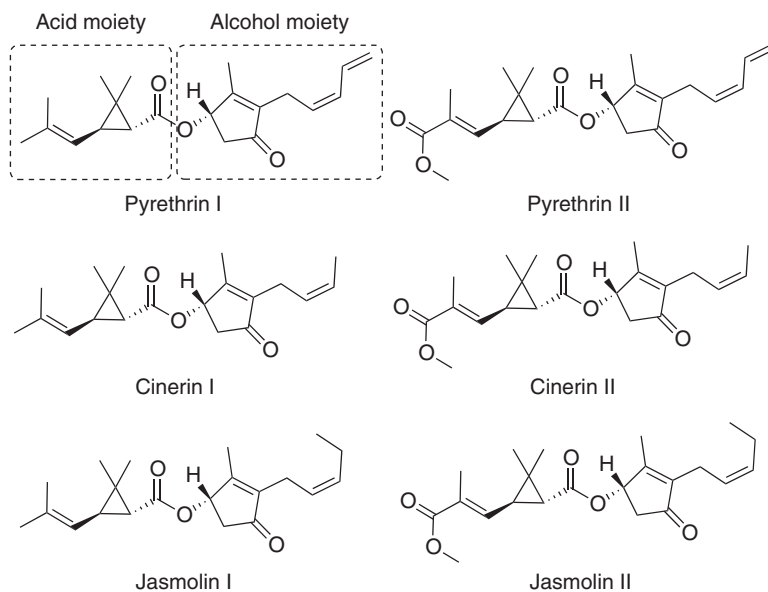


Figure 7.8 Chemical structure of natural pyrethrins.

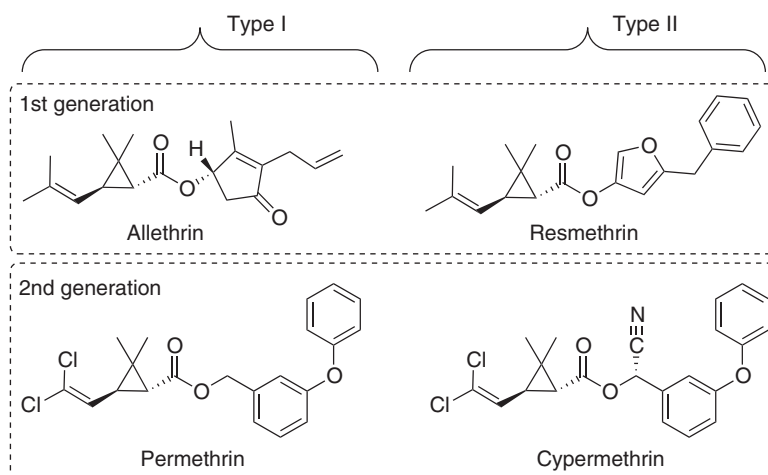


Figure 7.9 Chemical structure of 1st and 2nd generation of synthetic pyrethroids.

of the phenoxide units and are relatively volatile compounds that may vaporize in warm areas.

7.3.7 Triazines

Triazines are a group of pesticides, used mainly as herbicides with a wide range of uses. They are moderately soluble in water and difficult to eliminate from wastewater. Some common triazines are shown in Figure 7.11.

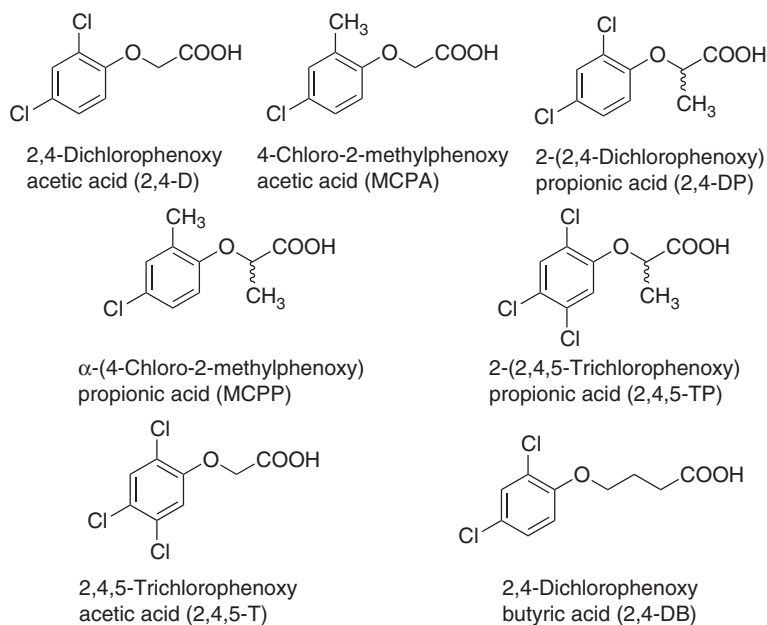


Figure 7.10 Chemical structure of some phenoxide herbicides.

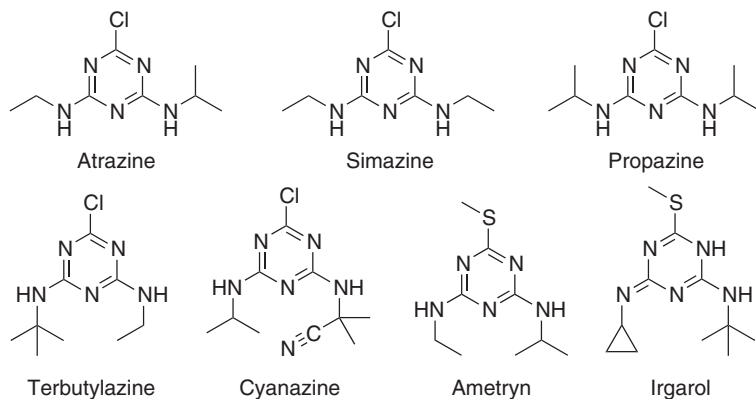


Figure 7.11 Chemical structure of triazine group of pesticides.

Atrazine is one of the most widely used pesticides worldwide [8]. High levels of triazines (primarily atrazine) in contaminated waters have been associated with increased harmful effects on wildlife, and potential health hazards for humans. Although some studies have shown these to cause mammary cancer in laboratory rats [9], there are relatively little scientific data exploring the relationship between simazine or cyanazine and human breast cancer [10, 11].

7.3.8 Uracils and Ureas

Both have similar uses and their modes of action have many features in common, inhibiting the ability to photosynthesize undesirable herbs. They are

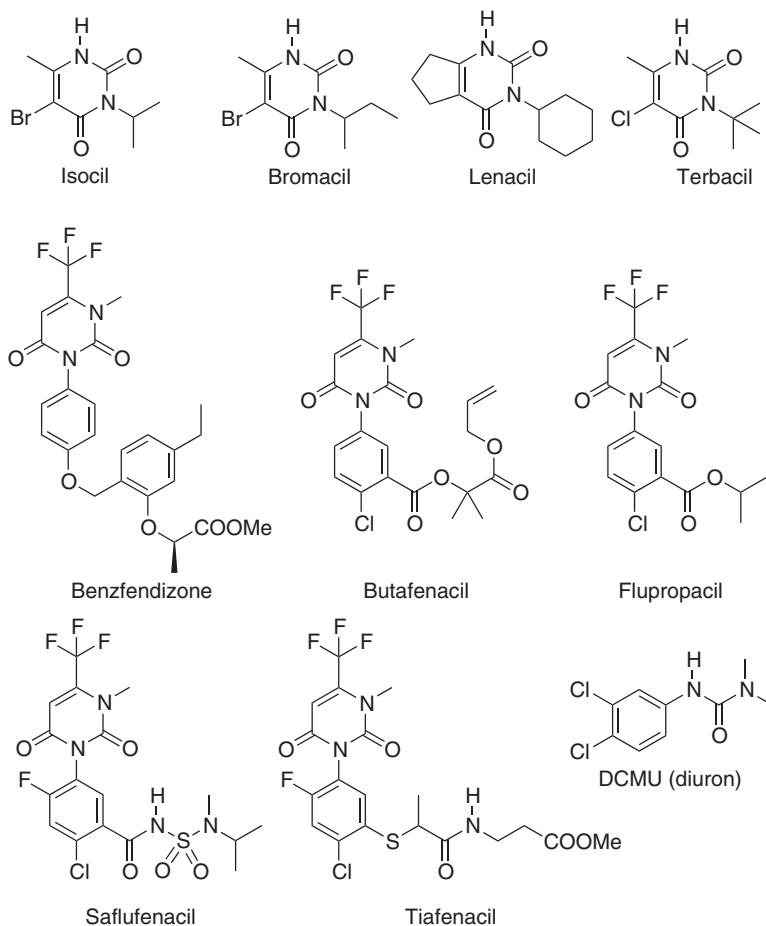


Figure 7.12 Chemical structure of main uracil and urea herbicides.

applied primarily to soil as pre-emergence herbicides, but they also provide post-emergence control for certain plants. Bromacil and diuron are widely used uracil and urea herbicides, respectively (see Figure 7.12).

7.3.9 Azoles and Related Compounds

This group of pesticides contains at least a five-membered heterocyclic ring such as imidazole or triazole (with two and three nitrogens, respectively), thiazole with a sulfur atom in azole ring, oxazole with oxygen in azole ring, and pyrazole with two adjacent nitrogens in azole ring (see Figure 7.13). Imidazole derivatives can be used as fungicides with systemic action against phytopathogens fungi applied on post-harvest fruits, seed dressing, or foliage.

Benzimidazoles are bicyclic compounds formed by a fused benzene and imidazole rings (see Figure 7.14). These compounds are widely used for treating parasitic infections and as systemic fungicides, to control pre-harvest diseases

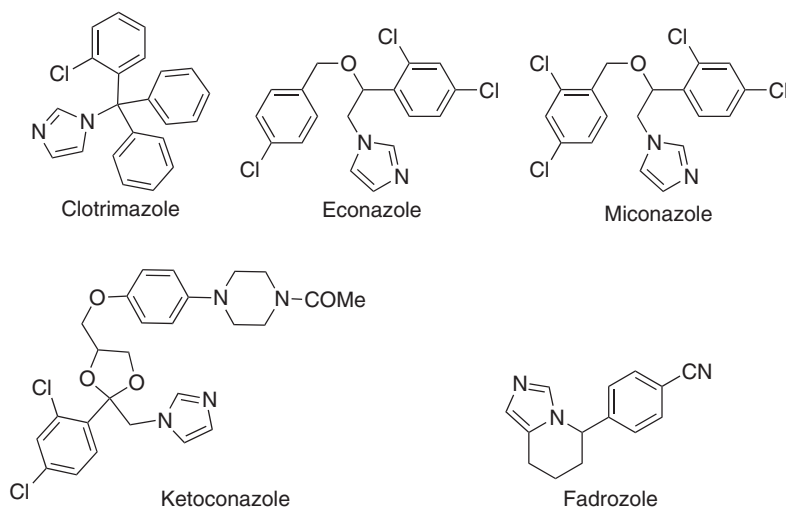


Figure 7.13 Chemical structure of main imidazole pesticides.

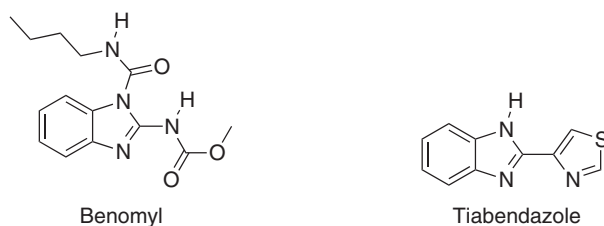


Figure 7.14 Chemical structure of main benzimidazoles.

and post-harvest spoilage during storage and transportation in the form of their insoluble salts [12]. For example, benomyl is a fungicide that is used selectively against microorganisms, especially earthworms.

Thiabendazole is a benzimidazole derivative used as a fungicide to control mold, blight, and other diseases in fruits and vegetables, and as an antiparasitic to control roundworms hookworms, and other helminth species that cause diseases in wild animals, livestock, and humans.

Triazoles are one of the largest classes of fungicides. The first triazole launched was triadimefon, by Bayer in 1973, followed by many other fungicides of this family, because they have shown high efficiency as demethylation inhibitors. Newer and intrinsically more active triazoles, have been marketed, and examples of these fungicides are described in Figure 7.15.

7.3.10 Morpholine Derivatives

They are fungicides used for control of cereal diseases, powdery mildew on vegetables and grapes, and sigatoka of banana. Such compounds are often referred to as sterol biosynthesis inhibitors (see Figure 7.16).

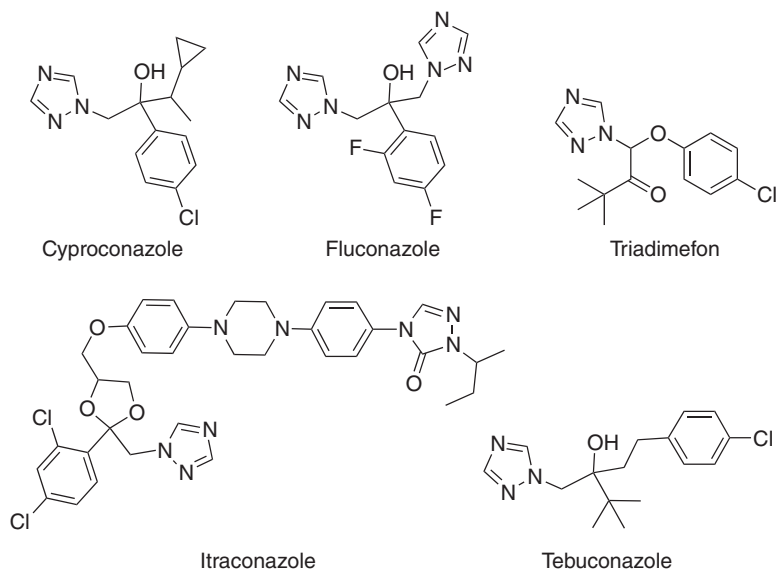


Figure 7.15 Chemical structure of main triazoles fungicides.

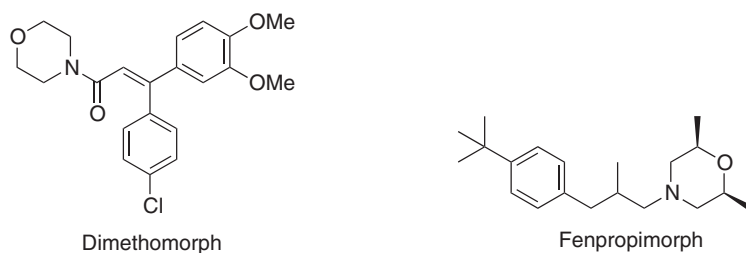


Figure 7.16 Chemical structure of main morpholine fungicides.

7.3.11 Bipyridines

4,4'-Bipyridine (4,4'-bipy) is used mainly as a precursor to the *N,N'*-dimethyl-4,4'-bipyridinium dication commonly known as paraquat (see Figure 7.17). These species are redox active, and their toxicity arises from their ability to interrupt biological electron transfer processes. Bipyridines are colorless solids, which are soluble in organic solvents and slightly soluble in water.

Paraquat is one of the most widely used herbicides. This salt is quick-acting and non-selective, killing green plant tissue on contact. It is also toxic to human

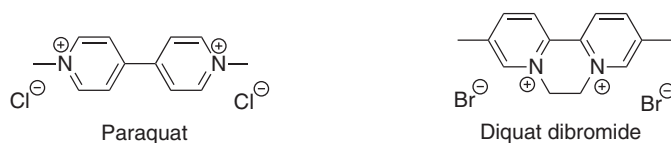


Figure 7.17 Chemical structure of paraquat and diquat dibromide.

beings and animals. It is linked to the development of Parkinson's disease [13], and today is among the most commonly used herbicides. In the United States, paraquat is available primarily as a solution and classified as "restricted use," which means that it can be used by licensed applicators only. In the EU, paraquat has been forbidden since 2007.

7.3.12 Amides

Since the first synthesis of carboxin in 1966, amide fungicides have also been used for controlling plant diseases for more than 50 years. Amide derivatives have become a research hotspot in the development of pesticides because of their high-efficiency active features and broad spectrum of antifungal, insecticidal, and herbicidal bioactivities. Currently, some amide derivatives have been developed and commercialized as pesticides. Mepronil, flutolanil, and tiadinil are known for their ability to protect certain plants from severe diseases and pests (see Figure 7.18).

7.3.13 Neonicotinoids

Nicotine is a colorless or pale-yellow oily liquid obtained mainly from two species *Nicotiana tabacum* and *N. rustica*. Because of its high volatility, it is used mainly as a fumigant. In agriculture, nicotine is used as nicotine sulfate which acts as a stomach poison.

Neonicotinoids are a new class of insecticides derived synthetically from nicotinoids (see Figure 7.19). The first-generation neonicotinoid insecticides as exemplified by imidacloprid (introduced in 1994), the second generation as exemplified by thiacloprid and thiamethoxam (introduced in 2001), and the third generation exemplified by dinotefuran (introduced in 2005) differ in their increased water solubility [14]. The most commonly used neonicotinoids include clothianidin, imidacloprid, and thiamethoxam (see Table 7.5). Imidacloprid also has a variety of other uses including lawn and garden products and topical flea medicines [15].

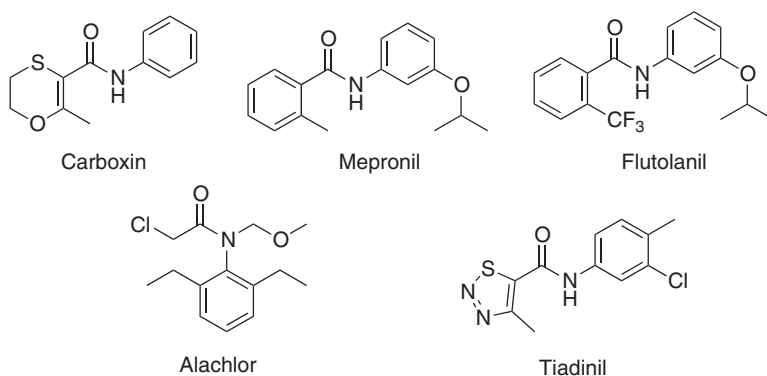


Figure 7.18 Chemical structure of amide fungicides.

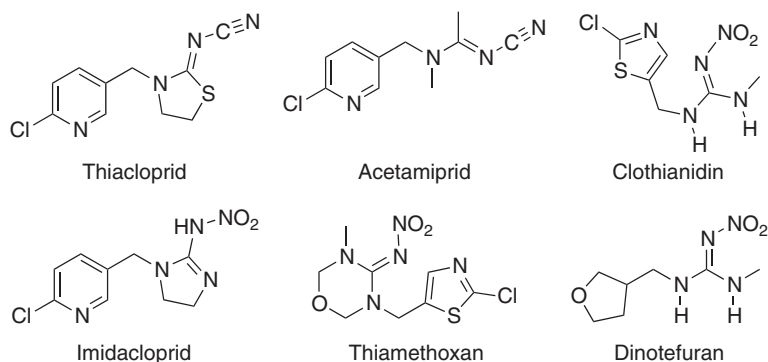


Figure 7.19 Chemical structure of neonicotinoid insecticides.

Table 7.5 Physicochemical properties of neonicotinoid insecticides.^{a)}

Compound	Solubility	Log K_{ow}
Acetamiprid	4250	0.8
Clothianidin	340	0.7
Imidacloprid	610	0.57
Thiacloprid	184	1.3
Thiamethoxan	4100	-0.13

a) Data taken from Ref. [25].

Recently, neonicotinoid insecticides have been the fastest growing class of insecticides [16]. Thus, in 2008 neonicotinoids comprised 24% of the insecticide market in Europe, equal to organophosphorus and carbamates combined, and 80% of the insecticidal seed treatments [15]. The chief reasons for this success are their selectivity and extreme efficacy in treating arthropod pests, their low fish and mammalian toxicity, and their versatility in application methods.

Neonicotinoid insecticides act agonistically on the arthropod's nicotinic acetylcholine receptors and are extremely toxic to aquatic insects [17]. They are very toxic to all aquatic arthropods [18] even at levels as low as $1 \mu\text{g L}^{-1}$ [19]. However, neonicotinoids pose a relatively low risk to fish and mammals [20]. Because of their solubility in water, all neonicotinoids are systemic insecticides and are applied as seed dressings in preference to foliar sprays [21]. Neonicotinoids are also receiving increased scrutiny since they have been linked to colony collapse disorder in bees [22]. As a consequence of their high water solubility and persistence in soil (see Table 7.5) they pose a risk of water contamination by runoff [23] and by leaching to the groundwater [24].

Since most neonicotinoids are fairly stable in the environment, it is possible that their occurrence may pose a threat to both aquatic and terrestrial organisms.

7.3.14 Other Classes of Herbicides

7.3.14.1 Pyridazines and Pyridazinones

The pyridazine structure is found within a number of herbicides such as credazine, pyridafol, and pyridate (see Figure 7.20), as well as the structurally related pyridazinones (see Figure 7.21).

7.3.14.2 Nitrile Herbicides

Nitriles such as bromoxynil, ioxynil, iodobonil, chloroxynil, bromobonil, dichlobenil, and pyraclonil (see Figure 7.22).

7.3.14.3 Dinitroanilines

Herbicides that are derivatives of dinitroanilines include benfluralin, butralin, chlornidine, dinitramine, dipropalin, ethalfluralin, fluchloralin, isopropalin, methalpropalin, nitralin, oryzalin, pendimethalin, prodiamine, profluralin, and trifluralin (see Figure 7.23). Oryzalin acts through the disruption (depolymerization) of microtubules, thus blocking anisotropic growth of plant cells. Trifluralin is one of the most widely used herbicides, being banned in the EU since 2008, primarily due to its high toxicity to fish and other aquatic life [26].

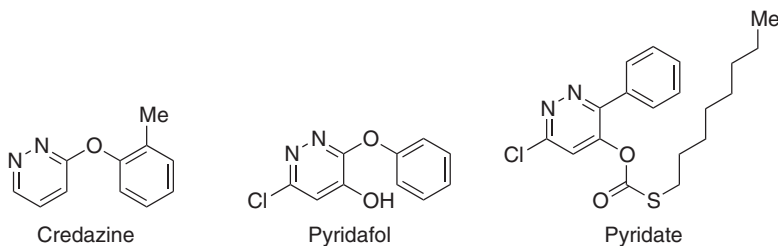


Figure 7.20 Chemical structure of pyridazine herbicides.

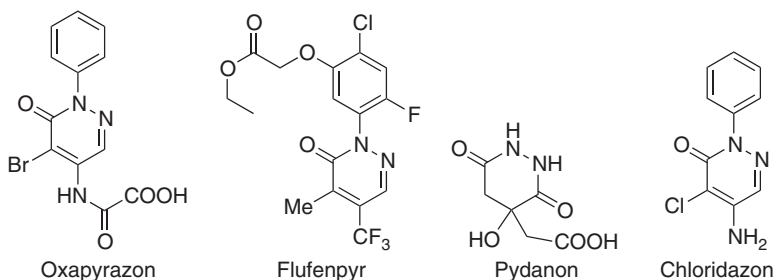


Figure 7.21 Chemical structure of pyridazinone herbicides.

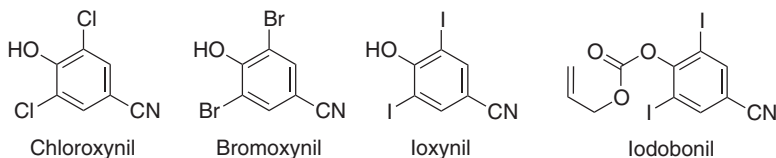


Figure 7.22 Chemical structure of nitrile herbicides.

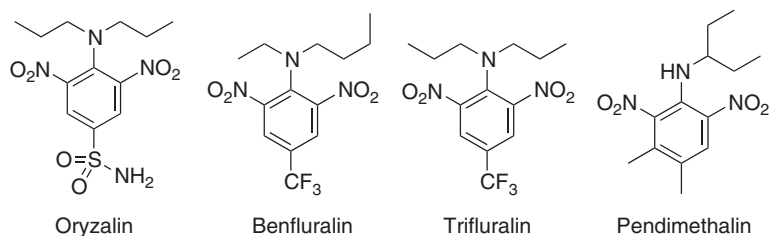


Figure 7.23 Chemical structure of dinitroaniline herbicides.

7.3.14.4 Pyridine Herbicides

The active ingredients of most concern are aminopyralid, clopyralid, and picloram. Other compounds of the same type are the following: clodinate, diflufenican, dithiopyr, florpyrauxifen, flufenican, fluroxypyr, halauxifen, haloxydine, picolinafen, pyriclor, pyroxsulam, and thiazopyr (see Figure 7.24).

7.3.14.5 Pyrimidines

Pyrimidinediamine herbicides such as tioclorim and iprymidam. Pyrimidinyloxybenzylamine derivatives such as pyribambenz-isopropyl and pyribambenz-propyl (see Figure 7.25).

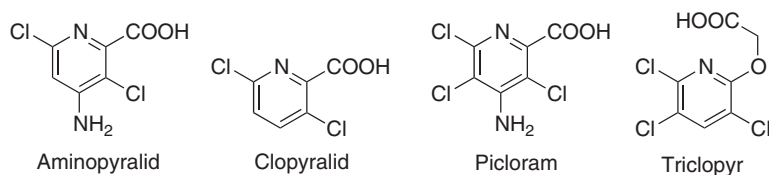


Figure 7.24 Chemical structure of pyridine herbicides.

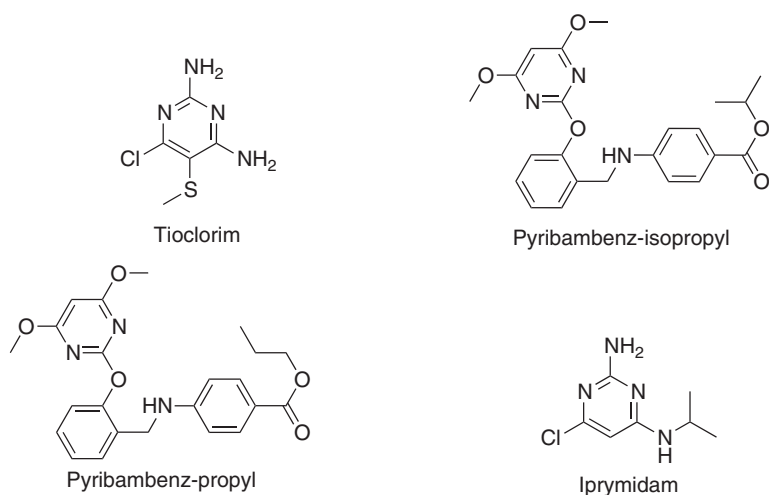


Figure 7.25 Chemical structure of pyrimidine herbicides.

7.4 Pesticides in the Environment

Despite different chemical structures and target organisms used as herbicides, insecticides, and fungicides, pesticides share a common use in their application over large areas in agriculture and urban settings. Therefore, their use represents a remarkable source of diffuse chemical pollution that is difficult to control.

Although pesticides are useful because they contribute to palliate hunger and improve the health conditions of the human population [27], in the last decades great controversy about their massive use has been raised due to their negative effects on the environment.

Pesticides have been well studied in terms of toxicity and environmental occurrence. Consequently, they have been considered in water quality policy (see Table 7.6). While some specific pesticides have been extensively regulated in surface water or drinking water, the use of other pesticides, for example, organochlorine pesticides, have even been banned in different countries. Currently, pesticides with lower environmental impact are commonly used.

Pesticides belong to a strictly regulated category of substances and, hence, large amount of data are available from regulatory testing for market authorization. This includes information from laboratory-based tests on aqueous hydrolysis, photolysis in water and air, biodegradability in soils and water-sediment systems under aerobic and anerobic conditions, and fate in soil.

With respect to toxicity, three variables are required to be taken into account [3]:

Maximum allowable residue levels in the United States: These are the tolerance levels for individual crops.⁷ Tolerances are defined by EPA as:

The maximum amount of a pesticide allowable in a food or feed product before it is considered adulterated, usually specified in ppm.

Human toxicity (long-term): This field contains three items; the hazard rating/long-term toxicity level (ppb)/toxicity type. This represents a relative long-term toxicity index for humans. The hazard ratings (extra-high, high, intermediate, low, very low) are indicators of the relative risk to humans.

Fish toxicity (threshold): This field contains three items; the hazard rating/toxicity threshold (ppb)/toxicity type, the hazard rating is based on “maximum acceptable toxicant concentration,” the soluble pesticide toxicity level for fish that is an indicator of the relative risk to the environment.

Some pesticides can negatively affect aquatic organisms. Carbaryl, an insecticide used on farms and lawns, can inhibit coral larval metamorphosis [29]. Metaxyl fungicide is toxic to algae and zooplankton [30], and metribuzin herbicide can harm corals’ symbiotic dinoflagellate algae, leading to impaired photosynthesis and bleaching [31].

⁷ These levels are for country-wide use and are reviewed and modified frequently to reflect regulatory changes, petitions by individual companies, or scientific developments; consequently, the tolerance values should be verified in the EPA website.

Table 7.6 Concentration of pesticides in drinking water regulated by EPA.^{a)}

Pesticide	Application	Potential health effect problems ^{b)}	MCL ^{c)} (mg L ⁻¹)	PHG ^{d)} (mg L ⁻¹)
Alachlor	Herbicide	Liver, kidney, and spleen	0.002	Zero
Carbofuran	Fumigant	Blood, nervous, and reproductive systems	0.04	0.04
Chlordane	Termicide	Liver and nervous system	0.002	Zero
Chlorobenzene	Agriculture	Liver and kidney	0.1	0.1
2,4-(D)	Herbicide	Kidney, liver, and adrenal	0.07	0.07
Dalapon	Herbicide	Minor kidney changes	0.2	0.2
DBCP	Fumigant	Reproductive, increase risk of cancer	0.0002	Zero
Dinoseb	Herbicide	Reproductive	0.007	0.007
Diquat	Herbicide	Cataract	0.02	0.02
Endothall	Herbicide	Stomach	0.1	0,1
Endrin	Insecticide	Liver	0.002	0.002
Glyphosate	Herbicide	Kidney	0.7	0.7
Heptachlor	Termicide	Liver	0.0004	Zero
Lindane	Insecticide	Liver, kidney	0.0002	0.0002
Methoxychlor	Insecticide	Reproductive system	0.04	0.04
Nitrite	Fertilizer	Infants ^{e)}	0.04	0.04
Oxamyl (vydate)	Insecticide	Nervous system	0.2	0.2
Pentachlorophenol	Wood treatment	Liver and kidney	0.001	zero
Picloram	Herbicide	Liver	0.5	0.5
Simazine	Herbicide	Blood	0.004	0.004
Toxaphene	Insecticide	Kidney, liver	0.003	Zero

a) Data taken from Ref. [28].

b) From long-term exposure above the MCL value.

c) Maximum contaminant level (MCL).

d) Public health goal (PHG).

e) Infants aged below six months could become seriously ill.

In principle, pesticides are registered for use only if they are demonstrated not to persist in the environment beyond their intended period of use (soil half-lives in the range of a few days to weeks). Nonetheless, residues of many pesticides are found ubiquitously in the natural environment in ng L⁻¹ to low mg L⁻¹ concentrations. For instance, surveys of groundwater and raw drinking water in industrialized countries typically detect 10–20 substances in recurrent

findings above 0.1 mg L^{-1} , the maximal accepted drinking water concentration for pesticides in many countries (e.g., see Table 7.6) [32].

7.4.1 Degradation and Transformation of Pesticides in Environment

Analogous to other organic compounds, pesticides share similar behavior in the environment. Therefore, they can be classified as persistent and non-persistent.

The degradation, transformation, or breakdown of pesticides involve different mechanisms, in living organisms, in the soil, water, or even in the air. Such transformations are diverse, chemically or enzymatically, or a combination of the two, by redox reactions or hydrolysis or it can take place upon exposure to radiation, especially UV frequencies. Degradation can take place by chemical processes, by biological transformations with the aid of microorganisms, or both.

Reactions in soil, water, or air are able to limit their permanence in the environment, and consequently their biological effects on the pest. It is assumed that the earlier steps of pesticide degradation occur by conventional organic reactions, while later steps involve microbials. The effect of pesticides and their degradation depends on physicochemical properties such as chemical stability, water solubility, or vapor pressure. Such properties determine the persistence and transport of pesticides and, consequently, the ability of living organisms to react.

Degradation of pesticides involves both biotic transformation and abiotic processes. The transformation processes that undergo a given pesticide is determined by its structural affinity to specific types of transformation, and to the exposed environmental conditions (see Figure 7.26) [5].

7.4.2 Pesticide TPs in the Environment

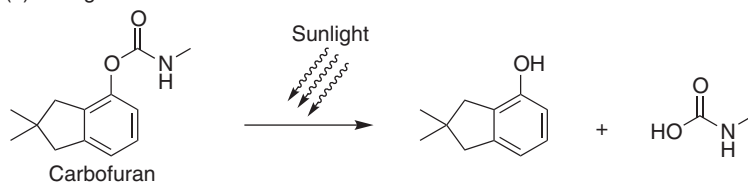
Recent studies have focused on their TPs because their hydrolysis, oxidation, biodegradation, or photolysis TPs can be present at higher levels in the environment than the parent compound, being as toxic as pesticides or even more so.

Pesticide TPs are occasionally more ubiquitous and abundant than their parent compounds. For instance, this has been reported for the chloroacetanilides metolachlor, alachlor, and acetochlor, and their respective ethanesulfonic acid (ESA) and oxalinic acid (OXA) derivatives; for cyanazine and its TPs, cyanazine acid, and cyanazine amide; and for glyphosate and its degradation product aminomethylphosphonic acid (AMPA) [33, 34].

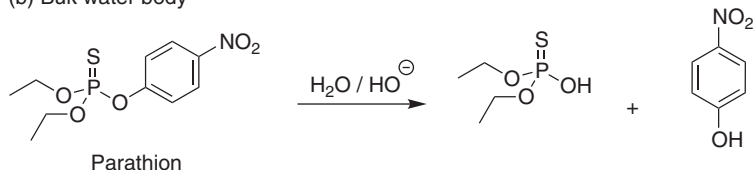
Groundwater is regularly monitored for the occurrence of a large number of pesticides in the United States and in European countries. However, only few pesticide TPs are usually included in these monitoring studies, and many others remain undiscovered. Several pesticide TPs are on the CCL-4: Oxirane, methyl, triphenyltin hydroxide (TPTH), acephate, dicrotophos, ethoprop, methamidophos, oxydemeton-methyl, permethrin, profenofos, tebufenozide, thiodicarb, tribufos, acetochlor, acrolein, bensulide, clethodim, dimethipin, diuron, metolachlor, oxyfluorfen, captan, clethodim, tebuconazole, thiophanate-methyl, vinclozolin, and ziram.⁸

8 <https://www.epa.gov/ccl/chemical-contaminants-ccl-4>.

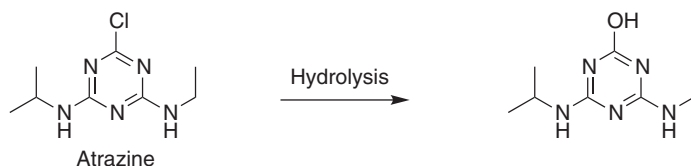
(a) Sunlight surface water



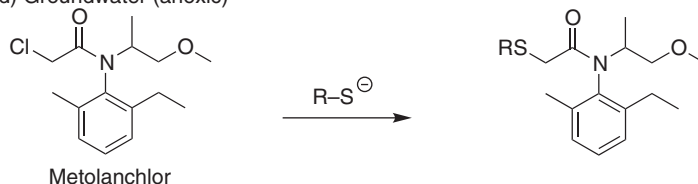
(b) Buk water body



(c) Groundwater (oxic)



(d) Groundwater (anoxic)

**Figure 7.26** Examples of pesticide degradation reactions in different compartments.

So far, the most investigated pesticide TPs are the dealkylated metabolites of atrazine. Table 7.7 summarizes the pesticide TPs found in groundwater and their concentrations [44].

The importance of monitoring pesticide TPs in groundwater has also been emphasized by Reemtsma *et al.* [41]. In the groundwater samples analyzed, the total pesticide TP levels were in the 0.2–6 $\mu\text{g L}^{-1}$ range [41]. Pesticide TPs have occasionally been quantified at levels above the groundwater-quality standard of 0.1 $\mu\text{g L}^{-1}$ values [44, 45].

7.4.3 Analysis of Pesticides

In the last few decades an increased tendency has developed for the substitution of persistent and hazardous pesticides by safer and environmentally benign products. A key problem is related to the degradation of pesticides to avoid bioaccumulation.

Table 7.7 Concentration (ng L⁻¹) of selected pesticide TPs found in groundwater.^{a)}

Parent compound	Pesticide TPs	Concentration	References
Acetochlor	Acetochlor ESA	14–1560	[33, 35]
	Acetochlor OXA	2009	[35]
Alachlor	Alachlor ESA	10–5690	[33, 35]
	Alachlor OXA	25–4170	[33, 35]
Atrazine	Desethylatrazine	0.3–1370	[33, 35–40]
	Desethyl-2-hydroxy-atrazine	0.5–90	[35, 37]
	Desethyl-deisopropylatrazine	620	[36]
	Didealkylatrazine	2680	[35]
	Hydroxyatrazine	170	[35, 36]
Atrazine, simazine	Desethylsimazine	0.2–1811	[33, 35, 36, 38, 40]
Chloridazon	Methyl-desphenylchloridazon (B-1)	11–1200	[37, 39–41]
	Desphenylchloridazon	177–13,000	[39, 40]
Chlorothalonil	R417888	8–55	[41]
	M12	275	[42]
Cyanazine	Cyanazine acid	440	[35]
	Cyanazine amide	110	[35]
	Desethylcyanazine acid	2190	[35]
Diuron	DCPMU	0–3	[41]
Fluopicolide, dichlobenil	2,6-Dichlorobenzamide	0.1–41,000	[37, 41–43]
Glyphosate	Aminomethylphosphonic acid (AMPA)	125–48,900	[34, 35]
Metalaxyl	M-CGA108906	275	[42]
Metalaxyl	M-CGA62826	50	[42]
Terbutylazine	Terbutylazine-2-hydroxy (MT13)	5–73	[41]
	Desethyl-terbutylazine (MT1)	2–266	[33, 36, 37, 39]
	Desethyl-2-hydroxy-terbutylazine	0.8–1.1	[37]
Triclopyr	3,5,6-TCP	9–14	[41]

a) Data taken from Ref. [44].

Therefore, another environmental risk has arisen, that is, the detection of residual pesticides in soil, water, and especially in food. Detectable amounts of pesticides remain in the environment, as modern analytical techniques have shown. For example, the EU carried out a study on 80,967 samples of a wide variety of unprocessed raw agricultural commodities and processed food products of member countries and products from third countries, which are subject to increased import controls (8270). More than 97% of food samples evaluated by the EFSA has shown pesticide residue levels that fall within legal limits, with just under 55% of samples free of detectable traces of these chemicals. The results of the dietary

exposure for population “the presence of residues found in the food products covered by the EU-coordinated monitoring programmes was unlikely to have a long-term effect on the health of consumers.” [46]

Reemtsma *et al.* [47] developed a multianalyte method for measuring 150 pesticide metabolites in groundwater and surface water using direct aqueous injection-LC/ESI-tandem mass spectrometry (MS/MS). A novel analytical approach has been developed by Ferrer *et al.* [48] for the quantitative analysis of a selected group of widely used pesticides⁹ that can be found at trace levels in olive oil and olives. The proposed methodology is based on matrix solid-phase dispersion, (with a preliminary liquid-liquid extraction in olive oil samples) using aminopropyl as sorbent material with a clean-up performed in the elution step with florisil, followed by MS identification and quantitation of the selected pesticides using both GC/MS in selected ion monitoring mode and LC-MS/MS in positive ionization mode.

Meanwhile, Souissi *et al.* [49] used LC/ESI-MS and GC/MS with electron ionization (EI) and chemical ionization (CI) to characterize the photolysis products of chloroacetamide pesticides.

7.4.4 Pesticides in Water

The most abundant pesticide TPs in groundwater derive from the chloroacetanilide herbicides acetochlor, alachlor, and metolachlor, the triazine herbicides atrazine and terbuthylazine, and the herbicides chloridazon and dichlobenil [33, 38, 39, 41, 42]. Desphenylchloridazon and *N,N*-dimethylsulfamide were the two most abundant compounds among the different synthetic organic compounds monitored in a pan-European groundwater survey, with maximum concentrations of 13 and 52 $\mu\text{g L}^{-1}$, respectively [39].

TPs derived from banned pesticides have consistently been detected in groundwater. This fact could be attributed to their long residence time in the subsurface or the slow release of their precursors from the soil [44]. This occurred with the dichlobenil¹⁰ that was detected at extraordinarily high concentrations (1200 $\mu\text{g L}^{-1}$) at a farm drinking water, drilled in a fractured rock impacted by a point source in Sweden [43]. Despite the ban of the herbicide atrazine in the European market since 2004, its TP desethylatrazine has frequently been detected in European groundwaters, and its concentrations occasionally exceed the EU standard of 0.1 $\mu\text{g L}^{-1}$ [38–40]. In a recent study in Germany, where the use of atrazine has been banned for 20 years, this pesticide and its TP, desethylatrazine, are almost always detected in the spring water of a karst aquifer in the low ng L^{-1} range [50]. Moreover, these results provide evidence of the long-term storage potential of karst aquifers, which is usually ignored in these rapid-flow transport systems.

Pesticides are another class of terrestrial pollutants that pose a threat to coral reefs and other coastal ecosystems. A study of the Hanalei river [51] found low waterborne concentrations of the insecticide dieldrin. Knee *et al.* [52], tested

9 Dimethoate, simazine, atrazine, diuron, terbuthylazine, methyl-parathion, methyl-pirimiphos, endosulfan I, endosulfan II, endosulfan sulphate, cypermethrin and deltamethrin.

10 2,6-Dichloro-benzamide (BAM-derivative).

carbaryl, metalaxyl, and metribuzin, three agricultural pesticides used in Hawaii. Carbaryl, an insecticide used in farms and lawns, can inhibit coral larval metamorphosis [29]. Metalaxyl, a fungicide, is toxic to algae and zooplankton [30], and metribuzin, an herbicide, can harm corals' symbiotic dinoflagellate algae, leading to impaired photosynthesis and bleaching [31].

7.5 An Example of National Survey: Pesticides in Italy

In Italy, the presence of pesticides in water resources became a national concern in the early 1980s when several studies reported the widespread distribution of a number of pesticides such as atrazine, simazine, and cyanazine, among others [27].

A remarkable contribution in assessing the occurrence of pesticides in Italian surface water and groundwater has been provided by the National Institute for Protection and Environmental Research [53]. This survey includes the monitoring of hundreds of pesticides in water resources throughout Italy during the biennium 2009–2010 in a total of 21,576 samples. A summary of the rivers and regional groundwaters where pesticides were investigated is given in Table 7.8 [54].

Available research reports pesticide contamination of surface water and groundwater more often in northern and central Italy (see Table 7.9).

Table 7.8 Italian rivers, lakes, and regional groundwaters (GW) where pesticides have been investigated.^{a)}

Pesticides	No. ^{b)}	Rivers	Lakes	GW-regions
Herbicides	79	Po, Arno, Not specified river of Tuscany, Seveso, Trionto, Passante, Sinni, Lese, Cardone, Telesse, Crocchio, Corace, Neto, Alaca	Maggiore, Fucino Plain, Lura Stream, Gordonella Stream, Livescia Stream	Lombardy, Piedmont, Friuli V.G., Veneto, Emilia R., Tuscany, Umbria, Marche, Abruzzo, Sicily
Fungicides	32	Po, Arno, Not specified river of Tuscany	Fucino Plain	Piedmont, Veneto, Tuscany, Umbria, Abruzzo, Sicily
Insecticides	26	Po, Arno, Not specified river of Tuscany, Corace, Neto, Alaca, Trionto, Passante, Sinni, Lese, Cardone, Telesse, Crocchio		Piedmont, Veneto, Tuscany, Umbria, Sicily
Algicides	1			Marche

a) Data taken from Ref. [54].

b) Investigated pesticides.

Table 7.9 Maximum concentration of most detected pesticides in both surface water and groundwater.^{a)}

	Surface water (ng L ⁻¹)	Groundwater (ng L ⁻¹)
Alachlor	4400	10, 200
AMPA	167, 000	–
Atrazine	2800	2700
Azoxystrobin	–	18, 960
Bentazone	1800	16, 000
Cadusafos	24, 960	–
Carbofuran	1200	1200
Chlorothalonil	8700	4800
Desethyl terbutylazine	4750	3150
Dielchin	–	478, 030
Diuron	30, 000	100
Endosulfan sulfate	–	10, 710
Linuron	13, 130	100
Malathion	16, 000	–
Metalaxyl	1440	7500
Metolachlor	16, 470	12, 500
Oxadiazon	4000	7790
Pendimethalin	–	15, 360
Terbutylazine	70, 000	29, 050
Terbutryn	18, 000	–

a) Data taken from Ref. [54].

Readman *et al.* [55] analyzed several fungicides in the estuarine water of the Po river at 90 km from its mouth. Water from the Po river and adjacent canals was sampled 10 yrs later for pesticide determination by Pasti *et al.* [56]. Triazines and their metabolites were investigated in three minor rivers belonging to the Po river watershed by Benvenuto *et al.* [57]. Griffini *et al.* [58] monitored 45 pesticides (32 herbicides, 11 insecticides, 1 fungicide, and 1 acaricide) in the Arno river, during the 1992–1995 period. Herbicide concentrations in the same river were also investigated by Bono and Magi [59]. Sbrilli *et al.* [60] and Pacioni *et al.* [61] reported concentrations of pesticides in surface water and groundwater of Tuscany and the Fucino Plain (Abruzzo, central Italy), respectively. In southern Italy, surface waters from 10 rivers of the Calabria region were studied by Curini *et al.* [62]. Loos *et al.* [63] investigated the contamination of surface water and groundwater around the Maggiore lake, the second largest lake of Italy, by several CECs including polar herbicides (e.g., atrazine, atrazine-desethyl, simazine, terbutylazine, isoproturon, linuron and diuron). Concerning groundwater, Caracciolo *et al.* [64] sampled 20 surficial aquifers nearby farms with high agricultural activities in the provinces of Bergamo and Lodi (Lombardy, northern

Italy) to investigate the occurrence of the herbicides metolachlor and diuron. Soon afterward, Guzzella *et al.* [36] conducted a two-year monitoring campaign to evaluate herbicide contamination of surficial water in northern Italy. Otto *et al.* [65] collected water from 70 wells in alluvial aquifers north of northern Italy. Pesticides were also investigated in groundwater from aquifers of several regions of Italy by Fava *et al.* [66] and Fait *et al.* [67]. Laini *et al.* [68] reported concentrations of the herbicide terbuthylazine and desethylterbuthylazine in lowland springs of the Po river. A study of contamination of several aquifers of Marche (central Italy) was carried out by Sagratini *et al.* [69].

The four most ubiquitous compounds in surface water were in the following descending order: the metabolite of glyphosate AMPA, terbuthylazine, and terbuthylazine-desethyl. In groundwater, the pesticides most frequently detected were in the following order: the terbuthylazine metabolite terbuthylazine-desethyl, the atrazine metabolite atrazine-desethyl, terbuthylazine, and atrazine [53].

The highest concentrations in surface water have been observed for the herbicides terbuthylazine (70,000 ng L⁻¹) and metolachlor (16,470 ng L⁻¹) and the metabolite of glyphosate AMPA (167,000 ng L⁻¹) (Table 7.9). Whereas the highest concentrations in groundwater have been detected for the insecticide dieldrin (478,030 ng L⁻¹), the priority substance simazine (221,000 ng L⁻¹), the herbicide terbuthylazine (29,050 ng L⁻¹), the insecticide cadusafos (24,960 ng L⁻¹), the herbicides bentazone (16,000 ng L⁻¹), metolachlor (12,500 ng L⁻¹), and metalaxyl (7500 ng L⁻¹) (Table 7.9) [54]. Currently, both atrazine and simazine belong to the list of priority substances reported in the Directive 2008/105/EC [70]. Maximum admissible concentrations in surface water and in groundwater are 100 ng L⁻¹ for a single pesticide and 500 ng L⁻¹ for a mix of pesticides (Directives 2006/118/EC [45] and 2008/105/EC [70]).

Of the 139 pesticides that have been studied, 64 in surface water and 56 in groundwater have been observed to have concentrations higher than the environmental limits defined in the Directive 2008/105/EC (100 ng L⁻¹) [70]. According to ISPRA (2013) [53], pesticide residues belonging to different classes appeared in 30.5% of surface water samples and 21.8% of groundwater samples. These percentages clearly point to the serious state of Italian surface water and groundwater contamination by pesticides [54].

7.6 An Example of Pesticides in the Environment: Neonicotinoid Insecticides

The occurrence of neonicotinoids in a variety of environmental matrices such as soil, air, surface water, and groundwater is the result of different applications methods. Most of the neonicotinoids are applied in the soil either as granules or as seed-dressing during crop planting [71]. For example, it was reported that surface runoff has twice as high concentration of imidacloprid compared to the wettable powder [72]. Studies have also reported that neonicotinoids can persist in soils for more than a year and nearly 80 to 98% of residual neonicotinoids eventually enter surface water and groundwater [71].

Monitoring data for neonicotinoids in the environment is limited, with most studies analyzing only imidacloprid in wetlands [73, 74] and in streams [75]. These fears have been confirmed by several surveys from the United States [76], the Netherlands [77], Sweden [78], and Vietnam [79]. In these surveys, imidacloprid residues were detected in 89–100% of cases in surface waters. For thiamethoxam and acetamiprid, the scarce data available indicate a detection in 31% and 17% samples, respectively [73]. Typically, residue levels in surface waters are below $1 \mu\text{g L}^{-1}$. Concentrations of imidacloprid in groundwaters up to $1.53 \mu\text{g L}^{-1}$ have been found in Vietnam [79].

Neonicotinoids are fairly stable toward biotic and abiotic degradation processes. For example, they are stable under photolytic and hydrolytic conditions. Abiotic degradation mechanisms determine their bioavailability, degradation, volatilization, leaching potential, and transport to subsurface and surface environment [80]. In 2013, the European Commission adopted a proposal to restrict the use of three neonicotinoids (clothianidin, imidacloprid and thiamethoxam) for a period of 2 years, including their use for seed treatment. [81] The EPA has changed the level at which the tolerance is being established from the proposed level of 1.1 ppm to 1.0 ppm in order to harmonize with the Codex MRL [82].

HPLC in conjunction with different detectors [83–85], MS [86–88] has been used for the determination of neonicotinoid pesticides in water and food. Other analytical methods for neonicotinoids are currently available for measuring their residues in fruit, vegetables, and honey and other bee products [89]. The use of photochemical reactions in order to improve the sensitivity, selectivity, and simplicity of the fluorescence analysis has been reported [90–92].

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8

Lifestyle Products as Emerging Pollutants

8.1 Introduction

This group of synthetic organic compounds originates from people's lifestyle choices. The main ways by which these substances reach the groundwater are by landfill leachates and the infiltration of treated and untreated wastewater. Among the most representative "lifestyle" products are stimulants and food additives (artificial additives and preservatives). This chapter examines the problems caused by food additives, their classification, and the possible long-term toxicity of some additives.

8.2 Stimulants

Stimulants are psychoactive drugs that induce temporary improvements in either mental or physical functions or both, by enhancing the activity of the central and peripheral nervous systems. For example, enhanced alertness, awareness, wakefulness, endurance, productivity, motivation, locomotion, heart rate, blood pressure, and the perception of a diminished requirement for food and sleep. Many stimulants are also capable of improving mood and relieving anxiety, and some can even induce feelings of euphoria. Stimulants exert their effects through a number of different pharmacological mechanisms, the most prominent of which include facilitation of norepinephrine (noradrenaline) and/or dopamine activity, adenosine receptor antagonism, and nicotinic acetylcholine receptor agonism.

Stimulants are used both individually and clinically for therapeutic purposes in the treatment of a number of indications. Classifying stimulants is difficult, because of the large number of classes the drugs occupy, and the fact that they may belong to multiple classes.

Caffeine (see Figure 8.1) is a stimulant compound belonging to the xanthine class of chemicals that are naturally found in coffee, tea, and to a lesser degree in cocoa or chocolate. It is also included in many soft drinks and in larger amounts in energy drinks. Caffeine is the world's most widely used psychoactive drug and by far the most common stimulant. It is also included in some pharmaceutical preparations, usually with the purpose of either enhancing the effect of the primary ingredient, or for reducing one of its side-effects (especially drowsiness). Tablets containing standardized doses of caffeine are also widely available.

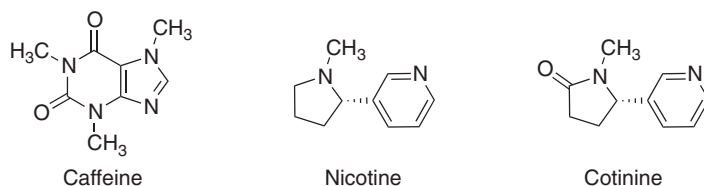


Figure 8.1 Structure of some central nervous system stimulants.

Nicotine (see Figure 8.1) is the active chemical constituent in tobacco, which is available in many forms, including cigarettes, cigars, chewing tobacco, and smoking cessation aids such as nicotine patches, nicotine gum, and electronic cigarettes. Nicotine is used widely throughout the world for its stimulating effects.

Caffeine and nicotine have proved to be ubiquitous in groundwater from aquifers impacted with treated wastewater via direct recharge or land irrigation [1–3].

8.2.1 Caffeine

Caffeine (see Figure 8.1), a naturally occurring xanthine alkaloid compound present in more than 60 plant species [4], is a central nervous system stimulant. The most widely used psychoactive drug in the world [5], it is found in a variety of beverages and food products and in many PCs [6].

About 90% of North American adults consume caffeine daily, mainly in the form of coffee, tea, or caffeinated soft drinks [7]. The average daily caffeine consumption per person in the United States has been estimated in the 140–210 mg d⁻¹ range [6, 8]. In Europe, adults consume an average of 37–319 mg d⁻¹ of caffeine.

8.2.1.1 Caffeine in the Environment

The sources of caffeine in water are primarily anthropogenic. The majority of ingested caffeine is converted to one or more secondary metabolites [9]. A small portion (0.5–10%) remains intact, which is excreted in the urine [6, 9, 10]. Thus, caffeine can enter the wastewater stream either through urine [6] or when caffeine-containing products, such as caffeinated beverages, coffee grounds, and other food and PC products are disposed off through household plumbing and sewer systems [11].

How caffeine loads to natural waterways from WWTP discharge is ultimately a function of both consumption of caffeine, which is dependent on population and its consumption habits, and the elimination efficiency of local WWTPs [6]. WWTPs eliminate some of the caffeine, but the elimination efficiency can be quite variable. Removal efficiencies can vary depending on the treatment processes employed, age of the activated sludge, hydraulic retention time, environmental conditions such as temperature and light intensity, and physical properties including the adsorption capacity of compounds in the sludge [12, 13]. Removal efficiency for caffeine in WWTPs, employing secondary treatment ranging from 64% to 100% have been reported [6, 10, 13, 14]. Weigel

et al. [15] described a removal efficiency of only 13% in a WWTP when using mechanical filtration without biological treatment. Some of the earliest studies documenting caffeine in natural waterways were conducted by the United States Geological Survey (USGS) [16]. Elevated concentrations of caffeine were attributed to the large population in the Chicago metropolitan area.

In recent years, much attention has been devoted to the occurrence of caffeine in natural waters. It has been established that caffeine is now present in a wide variety of environments, including WWTPs effluents, groundwater, and remote mountain lakes [17]. While caffeine was commonly observed in groundwaters in Europe, it was rarely detected in United States aquifers [18]–[22]. Concentrations are typically in the ng L^{-1} range in many freshwater environments. In certain areas, levels appear to be sufficiently high enough to approach threshold toxicity values for aquatic biota. Primary locations of concern in urban areas are discharge points of treated wastewater. Although caffeine presents no large-scale threat as of now, further research is needed on the occurrence of caffeine in natural waters and its chronic toxicity to aquatic organisms [17]. Caffeine concentrations reached up to 505 ng L^{-1} in different aquifers [1, 23], and up to 4500 ng L^{-1} were reported in groundwaters in the United Kingdom [24]. This substance was measured at an average concentration of 13 ng L^{-1} in groundwaters that were used as drinking water sources in Europe [19]. Moreover, concentrations below 15 ng L^{-1} were also observed in waters used for bottled water in Spain [19, 25].

Caffeine TP, such as paraxanthine, 3-methylxanthine, 1-methylxanthine, and theophylline were also detected in groundwater. While TP concentrations were usually in the same range as those of their parent compounds, they were overall less ubiquitous [1, 2, 20, 21]. The primary pathways by which caffeine is transported anthropogenically to marine systems include effluent discharge from WWTPs either directly or via streams and rivers draining to the coast, contaminated groundwater, and storm water runoff. Of these, discharge from WWTPs has received the most attention [6, 26, 27].

The majority of the studies reporting caffeine from marine systems have been conducted over the past decade on estuaries or coastal bays near a major metropolis. These studies have focused largely on documenting its presence, for example, in one estuary, or bay, or in the vicinity of one population center, but have highlighted the fact that caffeine may persist in marine waters. The studies have documented low levels (ng L^{-1} to low $\mu\text{g L}^{-1}$ range) of caffeine (see Table 8.1) [14, 26, 30, 31].

Concentrations encountered in the coastal ocean ranged from below the reporting limit to 44.7 ng L^{-1} [32]. These values are similar to those reported in other open ocean marine systems (see Table 8.1). Higher caffeine concentrations have been reported in other types of marine systems, but these were from enclosed water bodies (e.g., estuaries and bays) in highly populated areas [10, 14, 26] or from areas near wastewater discharge [31].

It has been suggested that exposure to caffeine may exacerbate the effects of other environmental stressors on corals, making them more likely to undergo bleaching [33]. Studies in the United States [10, 26], Europe [6, 34] and Australia [35] have linked caffeine concentrations in ground and surface waters

Table 8.1 Locations and concentrations of caffeine in seawater.^{a)}

Location	Type of water	Concentration range ^{b)} (ng L ⁻¹)	References
North Sea	Sea	2–16	[28]
Mediterranean Sea	Sea	n.d.–5	[6]
Hanelai, Kauai, Hawaii	Bay	n.d.–10	[7]
Miami River, Florida	Estuary	22–41	[8]
Biscayne bay	Bay	n.d.–12	
Miami River, Florida	Estuary	13–68	[29]
Key Largo harbor, Florida	Canal system	5.7–52	
Looe key, Florida	Offshore reef	n.d.–29	
Boston harbor	Estuary	140–1600	[10]
Massachusetts bay, Massachusetts	Bay	5–71	
Tromso Sound, Norway; North Atlantic/Arctic Ocean	Ocean inlet; ocean (10 km from coastline)	17–87; 7–9	[15]
Guanabara Bay, Rio de Janeiro, Brazil	Bay	134–147	[30]
Sarasota Bay, Florida	Enclosed Lagoon	n.d.–166	[26]
Halifax, Pictou, and Cocagne watersheds, Nova Scotia, Canada	Estuary	n.d.–1400	[31]
Jamaica Bay, New York	Estuary	n.d.–5000	[14]

a) Data taken from Ref. [32].

b) n.d. = not detected.

to wastewater contamination and suggesting that this could be used as a wastewater tracer.

8.2.2 Nicotine

Nicotine is a potent alkaloid found in the family of plants *Solanaceae* and is a stimulant drug (a nicotinic acetylcholine receptor agonist). It is found in the leaves of *Nicotiana rustica*, the tobacco plant *Nicotiana tabacum*, *Duboisia hopwoodii*, and *Asclepias syriaca*, in amounts of 2–14%.

It constitutes approximately 0.6–3.0% of the dry weight of tobacco¹ and is present in the range of 2–7 µg kg⁻¹ in various edible plants [36].

Nicotine is a hygroscopic, colorless oily liquid that is readily soluble in alcohol, ether, or light petroleum. As a nitrogenous base, nicotine forms salts with acids that are usually solid and water-soluble. It functions as an antiherbivore chemical

1 Cigars: Health Effects and Trends. Smoking and Tobacco Control Monograph No. 9. NIH Pub. No. 98-4302, February 1998.

and therefore nicotine was widely used as an insecticide in the past and neonicotinoids such as imidacloprid are currently widely used (see Section 7.5). However, currently, nicotine, even in the form of tobacco dust, is prohibited as a pesticide for organic farming in the United States.²

8.2.2.1 Cigarettes in the Environment

In 2005, 360 billion cigarettes were smoked in the United States.³ Cigarette butts, the plastic litter, and remnants of smoked cigarettes are discarded in natural environments, streets, sidewalks, and other public areas. Some of these butts may then be carried as runoff to drains, making their way to rivers, lakes, and ultimately to the oceans and beaches [37]. Cigarette litters are made from cellulose acetate, a plastic which is technically biodegradable [38]. However, in practice, cellulose acetate is resistant to biodegradation to a considerable extent and can therefore persist in the environment for 18 months or more, even under ideal conditions for biodegradability [39].

The Keep America Beautiful Campaign reported in 2007 that cigarette butts comprise 25–50% of all collected litter items from roadways and streets.⁴ Data from the Ocean Conservancy show that in 2015, over three million cigarettes or cigarette filters were removed internationally from beaches and inland waterways as part of the annual International Coastal Cleanup (ICC).⁵ Cigarette butts are poisonous when ingested by living organisms, as evidenced by poison control center data, veterinary literature, and national reports [40].

In 2008, over a million pounds of toxic chemicals were released by tobacco product manufacturing facilities. The top five chemicals released were ammonia, nicotine, hydrochloric acid, methanol, and nitrate compounds.⁶ Some of these materials are designated by the EPA as toxic release inventory chemicals, meaning these waste products are considered hazardous [41].

8.2.2.2 Nicotine in the Environment

Cigarettes contain from 8 up to 20 mg of nicotine, the average amount in one cigarette being 12 mg. Nicotine is a toxic compound and more than 0.5 g of oral nicotine is required to kill an adult [42]. Studies showed that the substances that seep out of cigarette butts were acutely toxic to freshwater microorganisms, and the main causes of toxicity come from nicotine and ethylphenol [43].

Concentrations of nicotine reported in groundwater did not exceed 144 ng L⁻¹ [1], although concentrations up to 8070 ng L⁻¹ were reported in groundwaters

2 US Code of Federal Regulations. 7 CFR 205.602 – Nonsynthetic substances prohibited for use in organic crop production <https://www.law.cornell.edu/cfr/text/7/205.602>.

3 US Department of Agriculture. Tobacco Outlook Report, Economic Research Service, October 24, 2007. <http://usda.mannlib.cornell.edu/usda/ers/TBS//2000s/2007/TBS-10-24-2007.pdf>.

4 Beck, R.W. Final Report: Litter: A Review of Litter Studies, Attitude Surveys and Other Litter-related Literature, Keep America Beautiful, Inc., 2007. <http://infohouse.p2ric.org/ref/50/49409.pdf>.

5 Ocean Conservancy. International Coastal Cleanup 2015 Report: A Rising Tide of Ocean Debris and What We Can Do About It. Washington, DC; 2015. <http://www.oceanconservancy.org/our-work/marine-debris/2015-data-release/2015-data-release-pdf.pdf>.

6 The Right to Know Network. Toxic Release Inventory Database 312229: Other Tobacco Product Manufacturing Facilities, 2008.

in the United Kingdom [24]. The nicotine TP, cotinine (see Figure 8.1), was also detected in groundwater, and concentrations were usually in the same range as those of their parent compound [1, 2, 20, 21].

8.3 Food Additives

Food additives are substances that are intentionally added to food, without themselves being considered food in the ordinary sense of the term. The term “food additive” is defined differently by the food laws of different countries. For example, in the Codex Alimentarius, “food additive” means any substance not normally consumed as a food by itself, and not normally used as a typical ingredient of the food, whether or not it has nutritive value. This includes intentional addition to food for a technological (including organoleptic) purpose in the manufacture, processing, preparation, treatment, packing, packaging, and transport or holding of such food. The additive may be reasonably expected to result (either directly or indirectly) in the food or its by-products becoming a component of or otherwise affecting the characteristics of such foods. The term does not include “contaminants” or substances added to food for maintaining or improving nutritional qualities.⁷

According to Codex Alimentarius, an additive is a substance intended for use in producing manufacturing, processing, preparing, and transporting or holding food; including any source of radiation intended for such use, if such substance is not generally recognized, among experts qualified by scientific training ... to be safe under the conditions of its intended use ...” [44]

Food additives are indispensable for the production and processing of many foods. Some are essential for the economic production and distribution of foods. Additives ensure the general availability of high-quality food with a satisfactory shelf-life [45].

According to the USFDA, there are three reasons why ingredients are added to foods:

- 1) to maintain or improve safety and freshness;
- 2) to improve or maintain nutritional value;
- 3) to enhance taste, texture, and appearance.

In the EU, food additives, food enzymes, and food flavorings are also known as “food improvement agents,”⁸ and they are used to improve food for the following reasons:

- Food additives preserve, color, and stabilize food during its production, packaging, and storage.
- Enzymes have specific biochemical actions that serve technological purposes at any stage in the food preparation.

7 Joint FAO/WHO Food Standards Programme. Codex Alimentarius Commission: Codex Alimentarius, vol. 14 Food Additives, Food and Agriculture Organization of the United Nations, Rome 1983.

8 http://ec.europa.eu/food/safety/food_improvement_agents_en.

- Flavorings add or change the odor or taste to food.

According to Luck and von Rymon [45], the four basic reasons for using additives are the following:

- 1) to influence the nutritive value of food;
- 2) to improve the stability of food;
- 3) to affect the sensory properties of food;
- 4) to make certain technological processes possible.

8.3.1 Toxicology of Food Additives

Smoke and salt were probably the oldest two food additives (preservatives) used since prehistoric times to improve the taste of food from plant or animal sources. Some food additives introduced in the nineteenth century are still being used, for example, baking powder, benzoic acid, and saccharin. However, others do not comply with current toxicological requirements and have thus disappeared from food processing.

Some people still harbor an aversion to food additives, explained by the uncontrolled use of chemicals in food processing. However, today, food additives are authorized only if no harmful effects of any kind can be shown after extensive toxicological testing. Many additives have undergone more rigorous testing than some foods or food components [45].

However, to date, no internationally binding standards exist for the toxicological testing of additives. The most widely accepted guidelines are those laid down by expert committees of the WHO [46]. The U.S. regulations⁹ are also widely observed.

According to this guideline, additives are tested for their acute, subchronic, and chronic toxicity, as well as for carcinogenicity, mutagenicity, teratogenicity, and biochemical activity. As a matter of principle, a food additive should not be pharmacologically active at the concentration at which it is used.

Acute toxicity, expressed as LD₅₀, and subchronic toxicity, established by the so-called 90-day test, are only crude measures of the toxicological properties of a substance.

Chronic toxicity is more important. The specifications for food additives are far more stringent than those for drugs, because additives may be consumed continuously for a very long period of time. Also, with food additives, side effects are not considered acceptable risks.

Biochemical tests are performed to determine the extent to which a food additive is absorbed by the organism, the factors affecting its absorption, its distribution within the body, and the manner in which it is excreted. Four basic possibilities exist:

- 1) A substance is excreted quickly and unchanged. Examples are the sweeteners saccharin and acesulfame-K.

⁹ US Food and Drug Administration Bureau of Foods: Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food, Washington 1982.

Table 8.2 Acceptable daily intake (ADI) values of some food additives.^{a)}

Additive	ADI (mg kg ⁻¹ d ⁻¹)	Additive	ADI (mg kg ⁻¹ d ⁻¹)
Acesulfame-K	0–9	Cyclamate	0–11
Alginates	0–50	Erythrosine	0–2.5
Amaranth	0–0.75	Ethyl maltol	0–2
Ascorbic acid	0–15	Fumaric acid	0–6
Aspartame	0–40	Gallates	0–0.2
Azo-rubine	0–4	Nitrates	0–5
Benzoic acid	0–5	Nitrites	0–0.2
Butylated hydroxyanisole	0–0.5	Phosphates	0–70
Butylated hydroxytoluene	0–0.5	Quinoline yellow	0–0.5
Caramel	0–100	Saccharin	0–2.5
Cellulose ethers	0–25	Sorbic acid	0–25

a) Data taken from Ref. [45].

- 2) A substance is quickly metabolized within the body and excreted in this metabolized form. An example is the preservative benzoic acid, which is converted in the body to hippuric acid and excreted in this form.
- 3) A substance is utilized quickly as a nutrient. Some examples are the preservative sorbic acid and the sweetener aspartame.
- 4) A substance is excreted more slowly than it is absorbed and thus accumulates in the body. An example of this is boric acid, which is considered undesirable and is no longer used as a food additive.

Animal trials are conducted to determine the concentration to which an additive remains nontoxic. Expert WHO committees use this value to define the acceptable daily intake (ADI) by reducing it by a factor of 100. The ADI values of some food additives are given in Table 8.2.

The safety of all food additives that are currently authorized has been assessed by the Scientific Committee on Food (SCF) and/or the European Food Safety Authority¹⁰ (EFSA). Only additives for which the proposed uses are considered safe are on the EU list.

8.3.2 Global Regulation on Food Additives

Food-additive regulation is an area of prominence since the beginning of US food safety laws over 100 years ago. The regulation of food additives globally has been led for many decades by the most robust and distinct safety-assessment programmes currently in place as well as their predecessor organizations, which include the Joint FAO/WHO Expert Committee on Food Additives (JECFA), and

¹⁰ <http://www.efsa.europa.eu>.

the European Union Scientific Committee on Food; more recently, the European Food Safety Authority (EFSA), and the USFDA [44].

The U.S. process typically consists of three distinct activities including the estimation of dietary consumption, assessment of likely toxicity, and a risk-management decision regarding safety. By contrast, all “food additives” in the EU must be on an EFSA listing authorizing their use.

Like the United States, the EU requires listing of the food additives in the appropriate regulation once the safety assessment is complete, and the addition of additives to these regulations is handled by the European Commission. Currently, EU food additive uses are governed in regulations EU 1330/2008 (Common Procedures); EU 1333/2008 (Approved Food Additives); EU 231/2012 (Specifications and Limitations); EU 1332/2008 (Approved Food Enzymes); EU 1334/2008 (Approved Food Flavors). The regulation EU 1333/2008 established that the toxicity of food additives evaluated before 20th January 2009 must be re-evaluated by European Food Safety Authority (EFSA) [47].

8.4 Classes of Food Additives

There are thousands of ingredients that are used to make foods. The FDA maintains a list of over 3000 ingredients in its data base “Everything Added to Food in the United States,” many of which we use at home every day.

According to their purpose, food additives can be classified into four categories [45]:

- Add nutrients.
- Enhance the food’s appearance or taste.
- Keep the food ingredients from separating.
- Keep food from spoiling or from making people sick.

8.4.1 Substances with Nutritive and Other Dietary Effects

The human body requires regular supplies of about 40–50 nutrients if all bodily functions are to proceed smoothly. If even one of them is missing or present in insufficient amounts, deficiency symptoms result.

Vitamins and minerals (and fiber) are added to many foods to make up for those lacking in a person’s diet or lost in processing, or to enhance the nutritional quality of a food.

8.4.1.1 Vitamins and Provitamins

Vitamins are used as food additives for dietary reasons, when sufficient vitamins are not supplied by the food itself or when losses have occurred during processing. Vitamins may also be added when the body is unable to absorb sufficient amounts of the vitamins contained in food.

The controlled addition of vitamins to food is called vitaminization, and the addition to compensate for processing losses is revitaminization. Enrichment or fortification means the addition of vitamins beyond the natural content. Standardization means adjustment of natural variations.

Oversupply is harmful only with the fat-soluble vitamins A and D, because this can lead to so-called hypervitaminosis.

8.4.1.2 Amino Acids

Some amino acids are added to foods for technological reasons, for example, flavoring or flavor enhancers or baking aids. Their use as food additives for dietetic reasons is restricted to the essential amino acids, that is, those which the body cannot synthesize. These are added to foods for the same reason as vitamins are.

8.4.1.3 Minerals and Trace Elements

Minerals and trace elements are added to foods only in special cases. Iron salts are of some importance because iron is sometimes not absorbed in sufficient quantity from food. The same is true of calcium, magnesium, copper, and zinc salts. The importance of magnesium for the cardiovascular system encouraged the addition of magnesium to food. In areas where the iodine content of drinking water is low, sufficient iodine intake can be achieved by the addition of iodides and iodates to common salt.

8.4.1.4 Bulking Agents

Although bulking agents are inert substances with little or no nutritive value, they are used in reduced calorie foods to generate a feeling of satiety. Among the most commonly used bulking agents are the crystalline cellulose, polydextrose and the disaccharide alcohol isomalt, which have low calorie values.

8.4.2 Substances with Stabilizing Effects

Products with increased shelf-life are in demand for many reasons: the increasing extent to which food is produced industrially, higher food-quality specifications, contemporary shopping and consumption patterns, and for certain health reasons.

Food spoilage is not cost-effective, and it can make consumers extremely sick. Preservatives decrease bacterial, viral, or fungal growth and keep oils from going rancid. Preservatives also keep foods from changing color or losing their freshness. Jams, jellies, baked goods, cured meats, and oils all contain preservatives. Lactic acid, citric acid, and other agents control the pH of foods, reducing spoilage.

8.4.2.1 Preservatives

Preservatives are compounds that delay microbiological spoilage of food from bacteria, molds, fungi, or yeast. Not only do these act against visible spoilage of food, they also prevent the formation of toxins, especially those produced by bacteria and molds. The most common preservatives and their concentration in foods are summarized in Table 8.3.

8.4.2.2 Antioxidants

Antioxidants delay the oxidative spoilage of food. They interfere with the early stages of oxidative and autoxidative processes to prevent formation of unwanted

Table 8.3 Concentration levels of preservatives in foods.^{a)}

Preservative	Concentration (ppm)	Preservative	Concentration (ppm)
Sorbic acid and sorbates	500–2000	Formic acid and formates	3000–4000
Benzoic acid and benzoates	500–1000	Hexamethylenetetramine	20–200
Parabens and their sodium derivatives	500–1000	Nitrites	50–100
Sulfur dioxide and sulfites	200–2000	Nitrates	200–600
Biphenyl	50–70	Acetic acid and acetates	5000–30,000
Phenylphenol	10–12	Lactic acid	5000–10,000
Thiabendazole	3–6	Propionic acid and propionates	2000–3000

a) Data taken from Ref. [45].

reaction products. Antioxidants are substances that react quickly with oxygen and thereby quench it. They slow or prevent changes in color, flavor, or texture and delay rancidity.

Autoxidation is a particularly troublesome process with fats that contain unsaturated fatty acids, which can form highly odoriferous, unsaturated aldehydes. These cause the fats to smell and taste unpleasant. Because the autoxidation of fats proceeds via a radical mechanism, radical scavengers therefore constitute the most notable group of antioxidants. The most commonly used antioxidants in foods are sulfur dioxide and sulfites, ascorbic acid and ascorbates, isoascorbic acid, tocopherols, gallates, butylated hydroxyanisole (BHA), and butylated hydroxytoluene (BHT).

8.4.2.3 Synergists and Sequestrants

Sequestrants are compounds that form complexes with metal ions and thereby convert them into an inactive form. Of special importance is the inactivation of traces of heavy metals, such as copper and iron, which accelerate oxidative changes catalytically. Sequestrants used in combination with antioxidants are called synergists because their reaction with metallic ions indirectly supports the antioxidative effect. Compounds that regenerate spent antioxidants are also called synergists. The most frequently used synergists and sequestrants in foods are lactic acid, lecithin, lactates, citric acid and citrates, tartaric acid and tartrates, phosphoric acid and phosphates, and calcium, and sodium salts of ethylenediaminetetraacetic acid (EDTA).

8.4.2.4 Packaging Gases

Gases are an additive used in food in order to create modified atmospheres and thus aid the conservation of food. They serve as propellants, and help in aeration or create carbonation. Packaging gases are used essentially to exclude oxygen from stored food and thus primarily protect against oxidative changes. The main

packaging gases used in commercial food processing are carbon dioxide, nitrous oxide, argon, helium, and nitrogen, and mixtures of these.

8.4.2.5 Stabilizers

Stabilizers are substances that protect from, or counteract, changes in the structure of food which, in a broader sense, can be considered spoilage. Stabilizers include emulsifiers, thickeners, and gelling agents, foam stabilizers, humectants, anticaking agents, and coating agents.

Emulsifiers: are substances that facilitate, or may be essential to, the production of emulsions. Emulsifiers improve and stabilize the consistency of foods and sometimes their viscosity, texture, and feel in the mouth as well. They improve the shelf-life of some foods such as baked goods. The most notable emulsifiers commonly used in foods are lecithins; phosphates; diphosphates, triphosphates, and polyphosphates; sodium, potassium, and calcium salts of fatty acids; mono- and diglycerides of fatty acids; esters of mono- and diglycerides of fatty acids; sucrose esters of fatty acids; sucroglycerides; polyglycerol esters of fatty acids; propane-1,2-diol esters of fatty acids; sodium and calcium stearoyl-2-lactylate; and stearyl tartrate.

Thickeners: Thickeners are hydrocolloids that are water soluble or can be readily hydrated or dispersed. They form viscous solutions. The thickeners commonly used in food are polysaccharides of plant, microbial, or semisynthetic origin. The most remarkable thickeners commonly used in foods are alginic acid, alginates, propane-1,2-diol alginate; agar; carrageenan; carob gum; guar gum; tragacanth gum; acacia gum; xanthan gum; pectin and amidated pectin; cellulose ethers, starch, starch esters, starch ethers, and modified starches.

Gelling agents: Gelling agents combine with water to form pseudo gels or gels. They maintain or improve the structure, consistency, or elasticity of a food. The most important gelling agents used in food are gelatin, alginates, agar, carrageenan, and pectin.

Foam stabilizers: Foam stabilizers are used particularly in the baking and confectionery industries. They impart greater stability to foamy preparations. In sugar-containing preparations, hydrocolloids such as methyl cellulose and tragacanth can be used.

Clouding agents: Clouding agents are thickeners that increase the viscosity of a beverage and thereby retard or prevent the deposition of finely suspended particles.

Humectants: Humectants are added to food to maintain a predetermined moisture level. They thereby prevent excessive drying out, or any changes in texture associated with this, and hardening. The primary humectants are sorbitol and glycerol.

Anticaking agents: Anticaking agents maintain the flowability of formed, powdered, or fine-grained products by preventing caking and adhesion. The most important anticaking agents used in food are calcium stearate and magnesium stearate, silicon dioxide, silicates, talc, flour, starch, and for common salt, alkali-metal ferrocyanides.

Coating agents: Coating agents are compounds that are used to cover or coat foods, or that are added to food surfaces for their protection. They are distinct from packaging materials, which are not food additives. Coating agents are used to protect foods or their surfaces against undesirable changes, such as drying out and loss of aroma. Coatings are used mainly for citrus fruit, confectionery, meat products, and cheese. The most important coating agents used in food are waxes, resins, oils, cellulose esters or acetic acid esters of the mono-glycerides of edible fatty acids, and talc.

8.4.3 Substances with Sensory Effects (Organoleptic Substances)

Not only should food have a nutritive value and be stable, it should stimulate the appetite by its appearance, taste, and aroma. Some substances have properties that influence positively the senses of smell, taste, and vision before, during, and after the consumption of food. Foods naturally contain sensorially active compounds. However, many of these are volatile or unstable. They may, therefore, be lost during food processing and storage. The main purpose of food additives that produce sensory effects is to compensate for such losses as authentically as possible.

8.4.3.1 Coloring Agents

An attractively colored food stimulates the appetite more than a discolored one. Apparently, there is a relationship between the eye and the gustatory nerves. Another purpose of food coloring is to provide a more variable range of products, which is especially important in the confectionery industry. As a rule, coloring is used only for processed food with no color of its own or in which only residual amounts of color remain.

Coloring agents are distinguished on the basis of their solubility, that is, insoluble coloring, pigments, and water-soluble or fat-soluble coloring. Pigments are used mainly for surface coloration of confectionery; fat-soluble colorants for fatty foods such as margarine and cheese, and water-soluble colorants for foods with a high water content such as fruit products and beverages. Depending on their origin, coloring agents may be classified as self-coloring food, natural coloring, or synthetic coloring.

The most remarkable colourants commonly used in foods are curcumin; riboflavin; tartrazine; quinoline yellow; sunset yellow FCF; cochineal; carmoisin; amaranth; ponceau 4R; erythrosin; patent blue V; indigo carmine; chlorophyll and its copper complexes; green S; caramel; black PN; carbon black; carotenoids (carotene, annatto, bixin, norbixin, capsanthin, capsorubin, lycopene, β -apo-8'-carotenal and its ethyl ester); flavoxanthin, lutein, cryptoxanthin, rubixanthin, violaxanthin, rhodoxanthin, canthaxanthin; beetroot red; anthocyanins; titanium dioxide; iron oxides and hydroxydes; metals (Al, Au, Ag); and pigment rubine (lithol rubine BK).

8.4.3.2 Color Stabilizers

Color stabilizers help foods retain their natural color during processing and storage and prevent undesirable discoloration. Nitrates or nitrites stabilize the desired red meat color through formation of nitrosomyoglobin.

8.4.3.3 Bleaching Agents

Discoloration in light-colored food can be removed in some cases with bleaching agents. Sulfur dioxide and sulfites are effective color stabilizers for enzymatic oxidation processes because they are enzyme inhibitors.

8.4.3.4 Intense Sweeteners

Intense sweeteners are compounds with a far more intensely sweet taste than sugar. They can be synthetic or derived from plants. Because of their intense sweetness, they need to be added only in small amounts and do not contribute to the caloric value of food. Intense sweeteners are used in foods for three main reasons: because of their lack of calories, because they are not harmful to diabetics, and because they are cheaper than sugar.

The two traditional sweeteners, saccharin and cyclamate, were suspected of being carcinogenic. This led to the development of new sweeteners, including aspartame, certain other peptides, and acesulfame-K.

8.4.3.5 Nutritive Sweeteners

Nutritive sweeteners are non-carbohydrate materials with a degree of sweetness similar to that of sugar; they can be used as substitutes for sucrose, glucose, and other sugars. Similar to sugars, they are metabolized. The most frequently used nutritive sweeteners are polyols (sugar alcohols): sorbitol, xylitol, and mannitol.

8.4.3.6 Acidulants

Acidulants are used to impart a sour taste to foods in a controlled way. Besides being sour, most of them have a characteristic taste of their own. This can be desirable, for example, in the case of citric acid. Acids that taste only sour or nearly so are malic acid and orthophosphoric acid.

8.4.3.7 Substances with a Salty Taste

Common salt is the most widely used substance with a salty taste that is used in food.

8.4.3.8 Substances with a Bitter Taste

A bitter or slightly bitter taste in foods is desirable only in certain cases, generally in beverages. Quinine is used as an additive for tonic; hops resins, and extracts from hops and hops flowers are used as additives in beer. Caffeine, which is added to some cola beverages, also has a slightly bitter taste.

8.4.3.9 Substances with an Alkaline Taste

Among flavorings with an alkaline taste, the only one that has even a limited practical role is sodium hydroxide solution.

8.4.3.10 Flavor Enhancers

Flavor enhancers are compounds that particularly enhance certain tastes or reduce undesirable flavors without having an especially strong taste of their own. They harmonize taste components and make food preparations more palatable. In this context, the Japanese expression umami substances has

come into general use [48]. Important umami substances include glutamic acid and glutamates, as well as purine-5'-ribonucleotides, especially inosine, guanosine, and adenosine 5'-monophosphates. Lately, thaumatin has been of interest.

8.4.3.11 Spices and Flavorings

Certain materials, mostly of plant origin, have been used from ancient times to improve the flavor of food. These include spices, herbs, herb extracts, and essences. Aromatic compounds are substances with a more or less pronounced odor that impart a specific aroma to foods. Chemically pure compounds, as well as plant extracts and microbial metabolites or extracts, are used. Flavoring is classified as natural, nature-identical, and artificial. Natural flavorings are produced through purely physical processes, usually from plant material, or through microbiological processes. In many countries, synthetically produced substances that are chemically identical to the natural ones are called nature-identical. Artificial flavorings are synthetically produced substances that have not been found in any natural products suitable for human consumption.

8.4.3.12 Chewing-Gum Bases

Chewing gum bases, also called masticatory substances, are the underlying components of chewing gum. At body temperature, they must be plastic, but they must also offer a certain bite resistance. The main chewing gum bases include gums, natural and synthetic resins, synthetic polymers, paraffins, and waxes.

8.4.4 Substances as Processing Aids

The Codex Alimentarius defines processing aids as:

*“any substance or material, not including apparatus or utensils, and not consumed as a food ingredient by itself, intentionally used in the processing of raw materials, foods or its ingredients, to fulfil a certain technological purpose during treatment or processing and which may result in the non-intentional but unavoidable presence of residues or derivatives in the final product.”*¹¹

Processing aids have a special status among additives in the food laws of practically every country.

8.4.4.1 Extractants

Extractants are solvents used to extract certain components of food. This is done or so that the food can be freed of certain unwanted components. The most commonly used solvents are water, ethanol, and other lower aliphatic alcohols, as well

11 Joint FAO/WHO Food Standards Programme. Codex Alimentarius Commission: Codex Alimentarius, vol. 14 Food Additives, Food and Agriculture Organization of the United Nations, Rome 1983.

as hexane, other hydrocarbons, and in special cases, dichloromethane. Supercritical carbon dioxide has been used increasingly as an extraction solvent because of its good solvent properties and because it leaves no residue.

Carrier solvents are distinct from extractants and are used to work small amounts of other additives into a food, for example, to dissolve vitamins, antioxidants, or aromatic compounds.

8.4.4.2 Clarifying Agents

Clarifying agents speed up the separation of suspended matter from those beverages in which clarity is desired, such as wine and beer. They also attract colloids and precipitate them.

The main clarifying agents for food are bentonite, activated charcoal, gelatin, tannin, polyvinylpyrrolidone, casein, and caseinates.

8.4.4.3 Filter Aids

Filtration is facilitated by filter aids, which, on suitable supports, form a filter layer of appropriate pore size and maximum filtering capacity. These materials must be inert and should not contaminate the liquid to be filtered with any soluble compounds. The most commonly filter aids used in the food industry are kieselguhr and cellulose.

8.4.4.4 Propellants

Propellants are used in the production of aerosols. Whipping cream, frying and baking and mold release oils, as well as spice extracts are used in aerosol form. Carbon dioxide, mixtures of propane and butane, dinitrogen monoxide, and certain fluorohydrocarbons and mixtures of these are used as propellants.

8.4.4.5 Cooling Agents and Cryogenics

Cooling agents and cryogenics are substances with a low boiling point which, when in direct contact with foods, extract heat from them and thereby cool them. The oldest cooling agent is crushed ice, and it continues to be universally used in chilling fish and other marine products at sea. The use of cryogenics is more recent. The most common of these is liquid nitrogen which is sprayed onto food in special freezing tunnels. The advantage of liquid nitrogen is that the freezing process is particularly fast when oxygen is absent.

8.4.4.6 Mold-Release Agents

Release agents facilitate the removal of foods such as confectionery or baked goods from molds. The most common mold-release agents are lecithins, stearic acid, calcium and other stearates, and waxes.

8.4.4.7 Antifoaming Agents

Antifoaming agents prevent unwanted foam development that may occur during food processing. Dimethylpolysiloxane, fatty acid esters of sorbitan and ethoxylated sorbitan, and various emulsifiers are suitable for this purpose.

8.4.4.8 Acidity Regulators

Acidity regulators generate a pH that is favorable or even essential for certain food processes. They are used, for example, to optimize the activity of enzymes or preservatives. The action of some gelling agents also depends on a particular range of pH.

8.4.4.9 Emulsifying Salts

Emulsifying salts are necessary for the production of processed cheese. They inactivate calcium which is important for the stability of the cheese gel. The action of emulsifying salts causes the insoluble paracasein gel to be converted to homogeneously flowing paracasein sol. After the melt has cooled down, the sol reconverts into a gel which, however, remains homogeneous and is stable. The leading emulsifying salts used in food are citrates and ortho-, di-, or polyphosphates.

8.4.4.10 Dough Conditioners and Flour Improvers

Dough conditioners and flour improvers enhance the processing and baking properties of flour and dough. Basically, they affect the gluten in flour and balance variations in the flour, especially in enzyme activity. Both oxidizing and reducing compounds can be used as dough conditioners. Widely, dough conditioners include cysteine hydrochloride and ascorbic acid. Some countries also allow azodicarbonamide and bromates.

8.4.4.11 Leavening Agents

Leavening agents lighten baked products, mostly by releasing carbon dioxide. Carbon dioxide can be generated biologically (e.g., by yeast or sourdough) or chemically (by baking powder). The latter is a mixture of sodium hydrogen carbonate and an acid, for example, a solid organic acid such as tartaric or citric acid, or sour salts such as certain phosphates.

8.4.4.12 Enzymes

Enzymes are widely distributed throughout foods of plant or animal origin. They are involved in food spoilage and, therefore, must often be inactivated during food processing, usually by heat.

8.4.4.13 Microbial Cultures

Cultures of microorganisms resemble enzymes in their application and mode of action. Frequently, their activity is due to the enzymes released by these cultures into food. Cultures of microorganisms may be used if they do not produce toxins or other undesirable substances.

8.4.5 Dietary Supplements

Food or dietary supplements are concentrated sources of nutrients or other substances with a nutritional or physiological effect, designed to enrich the normal diet. Prevalent dietary supplements include vitamins, minerals, herbals and botanicals, amino acids, enzymes, and many other products. Popular supplements include vitamins D and E; minerals such as calcium and iron;

herbs such as echinacea and garlic; and speciality products like glucosamine, probiotics, and fish oils.

Scientific evidence shows that some dietary supplements are beneficial for overall health and for managing some health conditions. Supplements may be used to correct nutritional deficiencies or maintain an adequate intake of certain nutrients. However, in some cases, excessive intake of vitamins and minerals may be harmful or cause unwanted side effects. The USFDA does not determine whether dietary supplements are effective before they are marketed. The European Commission has established harmonized rules to help ensure that food supplements are safe and properly labeled. In the EU, food supplements are regulated as foods and the legislation focuses on vitamins and minerals used as ingredients of food supplements. The main EU legislation is Directive 2002/46/EC related to food supplements containing vitamins and minerals [49].¹²

8.5 Food Additives as Emerging Organic Contaminants

Assessment of the exposure to food additives is based on information on known or anticipated human exposure to the additive or toxicologically relevant components of the additive from food, and any other potential dietary sources.

Some food additives are considered to be oxidants or endocrine disruptors [50]. For example, triethyl citrate is used as a food additive to stabilize foams as well as for pharmaceutical coatings, and is also a plasticizer. Butylated hydroxyanisole and hydroxytoluene are used to preserve fat in foods. Other food additives include camphor, 1,8-cineole (eucalyptol), citral, citronellal, *cis*-3-hexenol, heliotropin, phenylethyl alcohol, triacetin, and terpineol [51].

8.6 Antioxidants in the Environment

BHA¹³ and BHT are common preservatives used in cosmetic formulations and in food products. BHA was present at concentrations up to 1600 ng L⁻¹ in groundwater in the United Kingdom [51], but this compound was not detected in US groundwaters [52]. Despite the known instability of BHT in aqueous solutions, and its low water solubility (0.6–1.1 mg L⁻¹) and relatively high Log K_{ow} values (5.1),¹⁴ it is very ubiquitous in the groundwater bodies investigated [1, 2]. Evidence of BHT persistence in the subsurface was provided by Cabeza *et al.* [2], who reported similar average concentrations in reclaimed water used for aquifer recharge and groundwater from recharge aquifer (213 ng L⁻¹ vs. 133 ng L⁻¹) [2]. BHT concentrations in an artificially recharged aquifer

12 <https://www.efsa.europa.eu/en/topics/topic/supplements>.

13 Mixture of two isomeric compounds, 2-*tert*-butyl-4-hydroxyanisole and 3-*tert*-butyl-4-hydroxyanisole.

14 Physical properties database. Fate Pointers Search Module of the Syracuse Research Company (SRC, Inc.); 2014 <http://esc.syrres.com/fatepointer>.

were between 62 and 455 ng L⁻¹ [1]. Similarly as for BHT, its main TP, 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde (BHT-CHO) was also ubiquitous in groundwater. However, the average BHT-CHO concentration (121 ng L⁻¹) was lower than that of the parent compound (356 ng L⁻¹) [53].

8.7 Artificial Sweeteners in the Environment

Artificial sweeteners are predominantly used in the food industry for the production of sugar-free low-calorie foodstuffs. Their widespread use is mainly because they do not cause any glycemic effect/insulin response or calorie intake once digested, and do not adversely affect the microflora of dental plaque [54]. Currently, saccharin, cyclamate, aspartame, acesulfame, sucralose, alitame, neotame, and neohesperidin dihydrochalcone are the leading artificial sweeteners (see Figure 8.2), exhibiting countless food-chemistry applications [54]. The use of artificial sweeteners is even reported in drugs and sanitary products [55, 56].

In 2007, the global market for artificial sweeteners reached \$5.3 billion, of which the United States and Europe currently make up 65%.¹⁵ Production

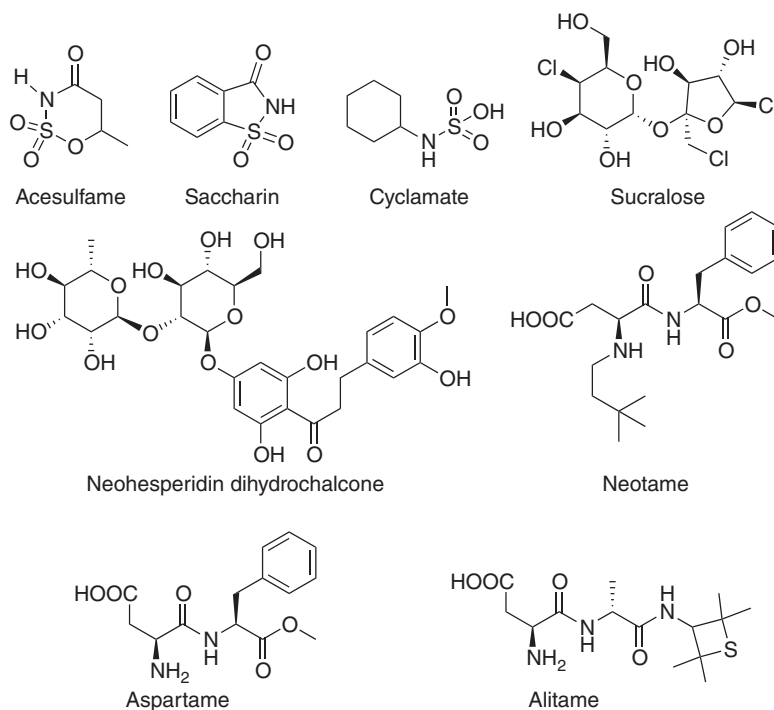


Figure 8.2 Structure of the main artificial sweeteners.

¹⁵ Bennett, D. The Intense Sweetener World, Ehrenberg Centre for Research in Marketing, 2008, <http://www1.lsbu.ac.uk/bus-ehrenberg/documents/High\LY1\textbackslash%20Intensity\LY1\textbackslash%20Sweeteners.pdf>.

volumes of artificial sweeteners vary between reports. Aspartame represents the largest artificial sweetener product segment globally, and it is the most frequently used artificial sweetener in the United States, and it is used in more than 6,000 food products [57].

Around 16,000 t of aspartame are produced annually in the United States for worldwide consumption [57]. Sucralose is a relatively new artificial sweetener that is now widely used throughout the world. It is synthesized by chlorinating sucrose, where three hydroxyl groups are replaced by chlorine atoms. Sucralose is heat stable, and therefore has replaced other artificial sweeteners (such as aspartame) for baking and is now widely used in soft drinks because of its long shelf-life [58]. The United States is also currently the largest market for sucralose, making use of more than 1500 t yr⁻¹, followed by Europe, with around 400 t yr⁻¹, as reported by a major Chinese company that recently entered into the sucralose market.¹⁶ In the Asian-Pacific market, the total volume output of saccharin, cyclamate, aspartame, acesulfame, sucralose, alitame, and neotame grew approximately 10% between 2009 and 2010, reaching approximately 109,000 t. Among sulfamates, cyclamate is currently the most produced artificial sweetener [55].¹⁷ with volumes reaching 57,800 t in 2010, followed closely by saccharin, aspartame, and acesulfame as the leading products in diet soft drinks, while sucralose is the key tabletop sweetener in the market.

8.7.1 Metabolism of Artificial Sweeteners

Following ingestion, a large percentage of saccharin, cyclamate, acesulfame, and sucralose pass unchanged from the human body [55, 59], whereas aspartame, alitame, neotame, and neohesperidin dihydrochalcone are eliminated after a larger degree of transformation [60].

Aspartame, in its dry form, is relatively stable, but unstable below pH 3, and is hydrolyzed to aspartylphenylalanine. Above pH 6, it is transformed to 5-benzyl-3,6-dioxo-2-piperazine acetic acid [61]. Alitame is soluble in water (approximately 13.1% w/v at 25 °C) and is relatively stable under heat (because of its unique amide group). Alitame, when hydrolyzed, is converted to alanine amide, aspartic acid, β -aspartic isomer (as impurity), and in the human body the *N*-glucuronide is the major metabolic product [60].¹⁸ Neotame is an *N*-substituted aspartame derivative [62] with its major degradation product being de-esterified neotame [62]. Neohesperidin dihydrochalcone is converted by humans anoxically to 3-(3-hydroxy-4-methoxyphenyl)propionic acid or 3-(3,4-dihydroxyphenyl)propionic acid [63]. Thus, the major metabolites of aspartame, alitame, neotame, and neohesperidin dihydrochalcone, rather than the parent compounds, should be expected to be present in the aquatic environment.

16 <http://www.foodnavigator-asia.com/Markets/Emerging-markets-and-sugar-prices-drive-sucralose-takeup-JK-Sucralose>.

17 CCM International, Survey of High Intensity Sweeteners in Asia Pacific, 2011 <http://www.cnchemicals.com;http://www.foodnavigator-asia.com/Markets/Asian-sweetener-market-on-the-rise-again-report>.

18 WHO Food Additive Series 35: Alitame. <http://www.inchem.org/documents/jecfa/jecmono/v35je11.htm>.

8.7.2 Occurrence of the Artificial Sweeteners in the Environment

From all artificial sweeteners, environmental research is especially focused on saccharin, cyclamate, acesulfame and sucralose, mostly for two reasons:

- 1) Their high determined concentrations in the aquatic environment (at $\mu\text{g L}^{-1}$).
- 2) Their partial (even if high for saccharin and cyclamate) or limited removal in wastewater and DWTPs [64–67].

Lange *et al.* [68] published an overview of LC-MS/MS and HRMS methods for measuring popular artificial sweeteners in aqueous environmental samples. Kokotou *et al.* [54] reviewed analytical methods (GC/MS, LC/MS, and IC/MS) for measuring artificial sweeteners in the environment. These authors summarize these methods, including sample preparation and chromatography techniques used, together with detection limits, recovery, and precision. New methods continue to be developed for analysis of artificial sweeteners. For example, Gan *et al.* [69] developed a novel method using ion-pair LC-MS/MS to measure common artificial sweeteners in river water, seawater, and drinking water, the quantification limits being in the $0.4\text{--}0.75\text{ ng L}^{-1}$ range.

Concentrations reported in the literature of artificial sweeteners in the environment are listed in Table 8.4.

All artificial sweeteners found in wastewater have also have been detected in groundwater [23, 54].

Recently, Lange *et al.* [68] reviewed the occurrence and fate of artificial sweeteners in the environment. These are extremely water soluble ($4\text{--}1000\text{ g L}^{-1}$) and hydrophilic ($\log K_{ow} < 0.91$) molecules, and therefore, they are expected to partition into the water phase.

Acesulfame is usually the most ubiquitous and abundant sweetener in groundwater [75–77]. It was found at concentrations up to $34\text{ }\mu\text{g L}^{-1}$ in shallow groundwater along urban streams in Canada [65]. Due to its environmental persistence, acesulfame is being investigated as a promising indicator of wastewater contamination [68, 75]. Overall, high concentrations of sweeteners, that is, occasionally reaching the $\mu\text{g L}^{-1}$ level, were found in groundwater impacted by wastewater or landfill leachates [78, 79]. For instance, saccharin concentrations up to $250\text{ }\mu\text{g L}^{-1}$ were measured in groundwater from a landfill site in Canada [78].

An extensive study on the distribution of sucralose in the aquatic environment of Europe was performed by Loos *et al.* [73], by screening stream and river waters from 27 countries. Data from the United Kingdom, Belgium, France, Switzerland, Italy, Spain, the Netherlands, Norway, and Sweden showed that sucralose concentrations in these countries were as high as $1\text{ }\mu\text{g L}^{-1}$ [73]. On the contrary, data from Germany and Eastern Europe showed that sucralose concentrations were lower than 100 ng L^{-1} [73]. It should be noted that the advantage of presenting capita values, in contrast to concentration values [73], is that these values are independent of the factors of discharge and population density [80].

Saccharin is largely excreted by animals and can be detected in manure at high concentrations (up to 12 mg L^{-1}), which are stable for at least 2 months of storage [70]. As a result of the application of manure in agricultural land, saccharin

Table 8.4 Reported concentrations of selected artificial sweeteners in the environment.

Environmental sample	Concentration (mg L ⁻¹)			
	Acesulfame	Cyclamate	Saccharin	Sucralose
Untreated wastewater, groundwater, surface water, and drinking water ^{a)} [55]				
Influents	12–43	10–65	3.9–18	2.0–9.1
Effluents	14–46		2.0–8.8	
Surface water	Up to 2.8			
Groundwater	4.7			
Tap water	2.6			
Wastewater and surface water ^{b)} [59]				
Influents	34–50	Up to 190	34–50	Up to 1
Rivers	0.27–2.7	Up to 0.32	0.01–0.35	0.01–0.11
Digested sewage sludge ^{c)} [70]				
Digested sludge	23–43	0.6–5.5	10–16	5.4–8.6
Drinking water ^{a)} [71]				
Source water				47–2,900
Finished water				49–2,400
Distribution system water				48–2,400
Open ocean waters ^{d)} [72]				Up to 392
European surface waters (stream and river waters) [73]				Up to 1
Wastewater ^{d)} [74]			Up to 5	0.8–1.8
Surface water ^{d)} [74]				Up to 1.8
Groundwater ^{d)} [74]				0.6–2.4

a) From DWTPs in the United States.

b) From Germany.

c) From Switzerland (Canton of Zurich).

d) In the United States.

has a high probability of residing in significant quantities in groundwater [70]. Acesulfame and sucralose are considered extremely persistent pollutants for their slow environmental degradation [67]. Moreover, saccharin, cyclamate, acesulfame, and sucralose are regarded as high-priority emerging contaminants because, although they are detected worldwide in a variety of environmental media, the monitoring of their presence is still not required by any existing regulations [67, 81].

Measurements of sucralose in the environment (including river water, groundwater, and coastal waters) have been reported, and research has expanded to include other artificial sweeteners, such as acesulfame, saccharin, cyclamate, aspartame, neotame, and neohesperidine dihydrochalcone. Because of its stability in the environment, sucralose has received a lot of attention as a potential tracer of anthropogenic inputs into environmental waters. LC/MS, GC/MS,

and ion chromatography (IC)/MS methods have been used for their analysis in environmental waters [66].

Tollefsen *et al.* [82] submitted a review on the presence, fate, and effects of sucralose in the aquatic environment. An extensive occurrence study of sucralose in U.S. drinking water was recently published by Mawhinney *et al.* [71].

Scheurer *et al.* [59] detected sucralose, acesulfame, saccharin, and cyclamate in wastewater from German STPs. Concentrations in wastewater influents ranged between 34 and 50 $\mu\text{g L}^{-1}$ for acesulfame and saccharin, respectively, up to 190 $\mu\text{g L}^{-1}$ for cyclamate, and below 1 $\mu\text{g L}^{-1}$ for sucralose. Acesulfame was removed in quantities up to 41% and sucralose by about 20%, whereas saccharin and cyclamate were removed by more than 90% [59]. Furthermore, Scheurer *et al.* [59] detected all four artificial sweeteners in German surface waters: acesulfame was found in concentrations exceeding 2 $\mu\text{g L}^{-1}$, saccharin and cyclamate were found at levels between 50 and 150 ng L^{-1} , and sucralose was mainly found from 60 to 80 ng L^{-1} . Then, Scheurer *et al.* [83] investigated the effectiveness of tap-water treatment in removing these four artificial sweeteners. They concluded that only saccharin and cyclamate could be completely removed by applying the treatments of river bank filtration and artificial groundwater recharge [83].

Buerge *et al.* [55] investigated the distribution of sucralose, acesulfame, saccharin, and cyclamate in wastewater, surface waters (from lakes and rivers), groundwaters, and drinking water of Switzerland. Concentrations ranging between 12–43 $\mu\text{g L}^{-1}$, 10–65 $\mu\text{g L}^{-1}$, 3.9–18 $\mu\text{g L}^{-1}$, and 2.0–9.1 $\mu\text{g L}^{-1}$ were found in influent wastewater samples for acesulfame, cyclamate, saccharin, and sucralose, respectively, whereas the respective concentrations in effluent wastewater samples were between 14 and 46 $\mu\text{g L}^{-1}$, <LOD–0.82 $\mu\text{g L}^{-1}$, <LOD–3.2 $\mu\text{g L}^{-1}$, and 2.0–88 $\mu\text{g L}^{-1}$ for acesulfame, cyclamate, saccharin, and sucralose, respectively [55]. Furthermore, all four compounds were found in surface waters (lakes and rivers), whereas only acesulfame was detected in groundwaters and drinking water. Acesulfame concentrations ranged from <0.01 $\mu\text{g L}^{-1}$ (LOD) up to 2.8 $\mu\text{g L}^{-1}$ in surface water samples. It was detected in 65 out of 100 analyzed groundwater samples at concentrations up to 4.7 $\mu\text{g L}^{-1}$. Acesulfame concentrations up to 2.6 $\mu\text{g L}^{-1}$ were measured in tap water samples taken from groundwater resources, and links between concentrations in groundwater samples and samples from the infiltrating river upstream of the pumping stations were indicated. This study highlighted the extensive distribution of acesulfame in the Swiss aquatic environment, concluding that elevated concentrations of acesulfame in groundwater may result primarily from infiltration of wastewater-polluted surface water through stream beds [55, 70]. Concentrations of saccharin in groundwater samples reaching up to 0.26 $\mu\text{g L}^{-1}$ were also reported by Buerge *et al.* [70], likely due to manure application in agricultural soils.

8.7.3 Artificial Sweeteners as Pollution Markers

For water-quality control purposes, the development of pollution indicators or pollution markers specific to wastewater effluents aids in determining the

source contributions in recreational waters or potable-supply sources. The characteristics of an ideal wastewater marker were described by Oppenheimer *et al.* [84]. The suitability of a variety of anthropogenic pollutants as wastewater indicators to sucralose were compared by examining occurrence data for 85 organic compounds in samples of effluents and surface waters with or without known wastewater influence. The results demonstrated the superior performance of sucralose as a potential indicator of domestic wastewater input in the United States.

While many compounds were detected in all of the effluent samples, sucralose was the only compound consistently detected in the surface waters with known wastewater discharges and it was notably absent in the samples without wastewater influence [84].

Recently, sucralose and acesulfame have proven to be reliable pollution markers [71, 84]–[87], and were also included with four other anthropogenic markers (carbamazepine, diatrizoic acid, 1*H*-benzotriazole, and 4-tolyltriazole) in a study by Scheurer *et al.* [87] to evaluate their predicability as wastewater markers.

8.7.3.1 Ecotoxicological Studies on Sucralose

The worldwide environmental distribution of sucralose at high concentrations, as demonstrated in the previous section, has channeled research exclusively in the last three years toward the assessment of the ecotoxicological impact of this particular artificial sweetener. Sucralose is considered safe for human consumption (the ADI for sucralose was set at 5 mg kg⁻¹ d⁻¹) [88–90], but its effects on the ecosystem have not yet been studied in depth, since limited ecotoxicological data are available in the literature. Thus far, sucralose has low bioaccumulation potential and negligible acute/chronic toxicity in aquatic organisms [91, 92] and does not appear toxic to plant growth [85]. In 2010, a major study was conducted by Hjorth *et al.* [93] to investigate the short-term effects (96 h) of sucralose in Arctic aquatic ecosystems. The factors assessed were egg production, hatching rate, food intake, and mortality of two species of Arctic copepods of the genus *Calanus*, *C. glacialis* and *C. finmarchicus*. The copepods were exposed to six different concentrations (0–50 µg L⁻¹) of sucralose, simulating the range of concentrations found in screening studies. The results showed that both species responded weakly to sucralose, but with *C. glacialis* being possibly slightly more sensitive than *C. finmarchicus* [93]. In 2011, a study was conducted by Huggett and Stoddard [94] to assess the effects of sucralose on the survival, growth, and reproduction of *Daphnia magna* and *Americamysis bahia* (mysid shrimp). The survival or reproduction of *D. magna* was not reduced even at concentrations as high as 61.8 g L⁻¹. The no-observable-effect concentration (NOEC) and lowest-observable-effect concentrations (LOEC) for *D. magna* were 1800 and >1800 mg L⁻¹, respectively. The survival, growth, and reproduction of the mysid shrimp were not affected by concentrations of 693 mg L⁻¹ of sucralose. The NOEC and LOEC for the mysid shrimp were 93 and >93 mg L⁻¹, respectively. Thus, the study concluded that the concentrations of sucralose detected in the environment were well below those required to elicit chronic effects in freshwater or marine water bodies [86].

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9

Industrial Chemicals as Emerging Pollutant

9.1 Introduction

While volatile organic compound (voc) and pesticides have been reported to leach into the environment over the past four or five decades, the discovery of other classes of synthetic organic compounds, for example, pharmaceuticals (PCs) and personal care products (PCPs), illicit drugs, perfluoroalkyl compounds, flame retardants (FRs), plasticizers, and preservatives, has been more recent. Many of them are environmentally persistent compounds. The recent development of highly selective and sensitive analytical techniques has been key in bringing these organic contaminants into focus [1].

Many different synthetic organic compounds are produced and used in large quantities worldwide for different purposes. Thousands of compounds are used as intermediates in the chemical factory industry (plasticizers, dyes, resins) or as food additives, antioxidants, surfactants, and detergents. Consequently, these substances are continuously released in the environment mainly due to industrial and domestic wastewater effluent discharges. To date, the occurrence of these contaminants of emerging concern (CECs) has been widely studied in wastewater and surface water.

The main effect associated with emerging contaminants is the alteration of functions in the endocrine system, that is, the contaminants act as endocrine disrupters. Some of these, which are known to cause serious problems to aquatic life, have already been classified as priority pollutants. Today, we know of around 100 industrial chemicals which, in addition to their desired chemical properties, also show estrogenic activity (see Chapter 5) [2]. Most of these estrogen-like chemicals are widely used POPs, which are ubiquitous in the environment and in biological samples. The most common endocrine disruptors found in the environment are: triclosan, tributyltin, E2, BPA, nonylphenol; the synthetic musks galaxolide and tonalide; the PCs paracetamol, ibuprofen, naproxen, diclofenac, and fluoxetine; PBDEs; and perfluorinated compounds (PFCs) [3, 4].

However, potential adverse effects of many others are unknown and they can therefore be considered as CECs. This chapter compiles data on relevant industrial chemicals, such as FRs, polychlorinated alkanes, plasticizers, antioxidants, chlorinate solvents, and perfluoroalkylated compounds (see Table 9.1).

Table 9.1 Relevant industrial chemicals.

Industrial chemicals	Compounds
Corrosion inhibitors	1,2,3-Benzotriazole, benzothiazol-2-sulfonic acid
Perfluoroalkyl compounds	Perfluorooctane sulfonic acid and its derivatives (PFOS)
Flame retardants	PBDE, 3,3',5,5'-tetrabromobisphenol A (TBBPA), C ₁₀ –C ₁₃ polychlorinated alkanes, tris(2-chloroethyl) phosphate
Plasticizers	Bisphenol A, phthalates: e.g., di-2-ethylhexyl phthalate (DEHP)
Alkylphenol ethoxylate surfactants	Nonylphenols (4-nonylphenol), octylphenol (4-(1,1',3,3'-tetramethyl-butyl)-phenol)
PAHs	Naphthalene, benzo[<i>a</i>]pyrene
VOCs	Benzene, CCl ₄ , 1,2-dichloroethane, 1,2-dichloroethene, dichloromethane, styrene, tetrachloroethene (PCE), toluene, CHCl ₃ , xylenes
Gasoline additives	Methyl <i>tert</i> -butyl ether (MTBE), dialkyl ethers
Antifouling compounds	Dibutyl tin ion, irgarol
Antioxidants	2,6-Di- <i>tert</i> -butylphenol
Others	2,4-Dinitrophenol, chloropicrin, pentachlorobenzene, pentachlorophenol, PCBs, hexabromocyclododecane

Some of them are standards and regulations established for CECs or by the USEPA, according to their toxicity and/or bioaccumulation potential. For example, Table 9.2 contains the standards and guidelines established for relevant industrial chemicals occurring in groundwater.

9.2 Perfluorinated Alkyl Substances (PFASs)

Perfluorinated alkyl substances (PFASs) is the collective name for a vast group of fluorinated compounds, including oligomers and polymers, in which all of the hydrogens of the hydrocarbon backbones are replaced by fluorine atoms. The group comprises several hundred compounds. They can be divided into the following groups: perfluorinated sulfonic acids, perfluorocarboxylic acids (PFCAs), fluorotelomer alcohols, high-molecular-weight fluoropolymers, and low-molecular-weight perfluoro alkanolamides. Two of these PFCs, that is, perfluorinated organic surfactants and fluorinated organic polymers such as PFOS and PFOA, have received the most attention.

PFCs are both hydrophobic and lipophobic, and they contain one of the strongest chemical bonds (C–F) known. The fluorine–carbon bonds confer very high thermal and chemical stability to these substances. They have been manufactured for more than 50 years, and because PFCs are inert, non-wetting, slippery, non-toxic, non-stick, fire resistant, and high-temperature resistant, they have been used in practically every aspect of human endeavor, ranging from cookware to fire-fighting foams, to paper coatings, textiles [9], stain/water/grease

Table 9.2 Standard and guideline values ($\mu\text{g L}^{-1}$) established for industrial chemicals for groundwater.^{a)}

Industrial chemical	USEPA ^{b)}	Europe ^{c)}	WHO ^{d)}
	MCL ($\mu\text{g L}^{-1}$)	AA/MAC ($\mu\text{g L}^{-1}$)	Guideline ($\mu\text{g L}^{-1}$)
Benzene	5	10/50	10
PBDEs	–	n.a./0.14	–
CCl_4	5	12/n.a.	4
1,2-Dichlorobenzene	600	–	1000
1,4-Dichlorobenzene	75	–	300
1,2-Dichloroethane	5	10/n.a.	30
1,2-Dichloroethene	700/100	–	50
1,1-Dichloroethene	7	–	–
Dichloromethane	5	20/n.a.	20
DEHP	6	1.3/n.a.	8
Naphthalene	–	2/130	–
Nonylphenols (4-nonylphenol)	–	0.3/2.0	–
Octylphenol (4-(1,1',3,3'-tetramethyl-butyl)-phenol)	–	0.1/n.a.	–
Pentachlorobenzene	–	0.007/n.a.	–
Pentachlorophenol	1	0.4/1	9
Benzo[a]pyrene	0.2	0.00017/ 0.27	–
PCBs	0.5	–	–
Styrene	100	–	20
PCE	5	10/n.a.	40
Toluene	1	–	700
Trichloroethene (TCE)	5	10/n.a.	20
Trichlorobenzenes	70	0.4/n.a.	–
1,1,1-Trichloroethane	200	–	–
1,1,2-Trichloroethane	5	–	–
CHCl_3	80	2.5/n.a.	300
Perfluorooctane sulfonic acid and its derivatives (PFOS)	–	0.00065/36	–
Hexabromocyclododecane (HBCDD)	–	0.5–0.05	–
Xylenes	10	–	500

a) Data taken from Ref. [5].

b) MCL: maximum contaminant level; Ref. [6].

c) AA/MAC: annual average/maximum allowable concentration; Ref. [7]

d) Ref. [8].

repellents (such as polytetrafluoroethylene and Teflon) in carpets and clothing, and in cooking utensils as nonstick coatings [10]. They are also used in the manufacture of paints, adhesives, waxes, polishes, metals, electronics, and caulks, as well as in greaseproof coatings for food packaging.

Two primary processes, electrochemical fluorination and telomerization, have been used to synthesize PFASs. The electrochemical fluorination products are composed of complex isomeric mixtures with rather consistent compositions: 70–80% linear and 20–30% branched isomers [11] while telomerization products are almost isomerically pure products, typical of linear geometry.

During 2000–2002, an estimated 5000 t yr⁻¹ were produced worldwide, with 40% of this in North America. Since 3M voluntarily phased out PFOS as well as its related products in 2000 and PFOA in 2002, the telomerization method became the predominant method to manufacture PFOA [12]. However, the manufacturing of PFASs in Asia, especially in China, has increased. It was reported that the production of PFOS was 200–250 t yr⁻¹ during 2008–2011 in China [13] and electrochemical fluorination method is still used by some manufacturers [14].

PFOS and PFOA are the two PFCs that have been produced in the largest amounts within the United States. PFOS is a perfluoralkyl sulfonate that is commonly used as a simple salt (such as potassium, sodium, or ammonium) or is incorporated into larger polymers. PFOA is a perfluoralkyl carboxylate that is produced synthetically as a salt. Ammonium salt is the most widely produced form, and PFOA as its ammonium salt is manufactured primarily for use as an aqueous dispersion agent and in the manufacture of fluoropolymers (used in a wide variety of mechanical and industrial components) such as electrical wire casings, fire- and chemical-resistant tubing, and plumbing seal tape. They are also produced unintentionally by the degradation of some fluorotelomers.

9.2.1 PFASs in the Environment

Because of their chemical structure, PFCs, including PFOS and PFOA, are chemically and biologically stable in the environment and resist typical environmental degradation processes, including atmospheric photooxidation, direct photolysis, and hydrolysis. As a result, these chemicals are extremely persistent in the environment, and some of the substances bioaccumulate in the environment [15].

When released directly to the atmosphere, PFCs are expected to adsorb to particles and settle to the ground through wet or dry deposition [16]. In their anionic forms, PFOA and PFOS are water-soluble and can migrate readily from soil to groundwater, where they can be transported long distances [17]. As a result, they are widely distributed across the higher trophic levels and are found in soil, air, and groundwater. PFOS has usually been detected at slightly higher concentrations than PFOA. The toxicity, mobility, and bioaccumulation potential of PFOS and PFOA pose potential adverse effects for the environment and human health. A number of related chemicals, referred to as “PFOS precursors” can transform or degrade into PFOS in the environment. PFOS is the final degradation product, and is not known to be subject to any further degradation in the environment or change in living organisms (i.e., metabolism).

In a pan-European survey, PFOS and PFOA were detected in 48% and 66% of the groundwater samples, respectively. PFOS was present at a maximum concentration of 135 ng L⁻¹, whereas PFOA did not exceed 39 ng L⁻¹ [18]. These levels do not exceed the maximum allowable concentration for inland surface waters set for PFOS in the EU (see Table 9.2). Slightly lower concentrations were reported

in the United States in groundwater, where concentrations of PFOS and PFOA were usually below 97 ng L^{-1} and 22 ng L^{-1} , respectively [19, 20]. A recent study provided evidence of the widespread pollution of PFASs in Tokyo. Median concentrations of PFOS and PFOA found in groundwater (5.7 ng L^{-1} and 8.5 ng L^{-1} , respectively) were similar to those measured in Europe [21].

Drinking water was the focus of a review on PFOA as an emerging drinking-water contaminant published by Post *et al.* [17] covering the impact of this contaminant on drinking water, human exposure and serum levels, toxicokinetics, and on potential human health effects. Drinking water was also the focus of an extensive PFC national screening study in France [22]. In that study, 331 source water and 110 finished drinking-water samples were collected from several regions in France, representing 20% of the national water supply. PFOA, and perfluorohexanoic acid (PFHxA) were predominant in the source waters. In finished drinking water, short-chain PFCAs were predominant. Another extensive study was conducted by Llorca *et al.* [23], who followed 21 PFCs throughout the entire water cycle¹ in 32 cities in Germany and Spain. The fate of PFOA and PFOS during different stages of drinking water treatment was the focus of a study by Flores *et al.* [24].

Another extensive study by Cai *et al.* [25] on PFCs involved their occurrence from the North Pacific Ocean to the Arctic Ocean. Seawater, sea ice core, and snow samples were collected along the eastern coast of Asia and the western and northern coast of Alaska. A total of 14 different PFCs were measured. Average concentrations of total PFCs in surface waters were 560 pg L^{-1} for the Northwest Pacific Ocean, 500 pg L^{-1} for the Arctic Ocean, and 340 pg L^{-1} for the Bering sea. PFOA and PFOS have been detected in concentrations of pg L^{-1} in remote regions of the Arctic caps. In addition, PFOS concentrations detected in the liver of the Canadian Arctic polar bear range from 1700 to more than 4000 ng g^{-1} [26, 27].

Landfill leachates [28], fire-training areas, and airports [20] constitute an additional two important sources of PFASs to groundwater. PFASs in landfill leachates were measured at concentrations up to $6 \mu\text{g L}^{-1}$ [28]. PFASs concentrations reported in groundwater beneath a military base were up to three orders of magnitude higher (in the mg L^{-1} range) than those measured in landfill leachates [29]. Landfill leachates were the focus of a study by Benskin *et al.* [30], who measured PFCs. Airports can also be a source of PFC contamination. De Solla *et al.* [31] carried out a study near Munro International Airport in Hamilton, Ontario, because unexpectedly high levels of PFCs, particularly PFOS, had been detected in a lake nearby.

9.2.2 Analysis of PFASs

PFOS and PFOA are commonly deposited in the environment as discrete particles with strongly heterogeneous spatial distributions. Unless precautions are taken, such distributions will cause highly variable soil data that can lead to confusing or contradictory conclusions about the location and degree of

1 Wastewater, river water, tap water, and mineral bottled water.

contamination. Proper sample collection, sample processing (which includes grinding), and incremental subsampling are required to gather reliable soil data.

PFOS and PFOA in anionic form can be extracted from environmental media by conventional methods using either acidification or ion pairing to obtain a neutral form of the analyte. Sample-preparation methods used for PFCs have included solvent extraction, ion-pair extraction, solid-phase extraction, and column-switching extraction [32]. Precursors and intermediate degradation products can be extracted using solvents [33]. Air samples may be collected using high-volume air samplers that employ sampling modules containing glass-fiber filters and glass columns with a polyurethane foam [34].

The analytical detection method of choice for PFOS and PFOA is currently high-performance LC–MS/MS, whereas both LC–MS/MS and GC/MS can be used for the determination of precursors of PFOS and PFOA. HPLC–MS/MS has enabled more sensitive determinations of individual PFOS and PFOA in air, water, and soil [35, 36]. EPA Method 537, Version 1.1, is an LC–MS/MS method used to analyze selected perfluorinated alkyl acids in drinking water.

The advancements in LC–ESI-MS/MS and LC–MS/MS has improved the analysis of PFOS and PFOA. Reported sensitivities for the available detection methods include pg m^{-3} levels in air, pg L^{-1} to low ng L^{-1} levels in water, and pg g^{-1} to ng g^{-1} levels in soil.

9.2.3 Toxicology and Regulation of PFASs

Due to the global detection of PFASs in different biological matrices, such as fish, birds, and mammals, even in remote Arctic wildlife [37], PFASs have received great scientific and regulatory scrutiny. Laboratory studies on animals have demonstrated that hepatotoxicity, immunotoxicity, and reproductive and developmental alterations are the main toxicological effects of PFOA and PFOS [38]. Many other studies have measured the PFAS concentrations in wild organisms to investigate the contamination levels and bioaccumulation potential of PFASs [39, 40], or to assess the health risk for human beings [41]. The wide distribution of PFCs increases the potential for bioaccumulation and bioconcentration as they are transferred from lower- to higher-trophic-level organisms. The bioaccumulation potential of PFCs grows with increasing carbon chain length [42]. PFOS is the only PFC that has been shown to accumulate to levels of concern in fish tissue. The ingestion of PFOA-contaminated water was found to cause adverse effects on mammary-gland development in mice [17]. One study indicated that exposure to PFOS can affect the neuroendocrine system in rats. However, the mechanism by which PFOS affects brain neurotransmitters is still unclear [43]. Both PFOS and PFOA have a high affinity for binding to β -lipoproteins and liver fatty-acid-binding protein. Several studies on animals have shown that these compounds can interfere with fatty acid metabolism and may deregulate the metabolism of lipids and lipoproteins.

Their use in a wide range of products has been reduced due to accumulating evidence of their toxicological effects and because they are now included in the Stockholm Convention. The USEPA has listed PFOA and PFOS on the CCL-4, a

priority list for consideration for future regulation in drinking water.² Six PFCs are also included in the USEPA's UCMR-3: PFOA, PFOS, perfluorononanoic acid (PFNA), perfluorohexane sulfonic acid (PFHxA), perfluoroheptanoic acid (PFHpA), and perfluorobutane sulfonic acid (PFBS).³ The National Toxicology Program is also studying PFOA and several other PFCAs and perfluorosulfonate acids (PFSAs) to better understand their toxicity and persistence in human blood [44]. While PFOS and PFOA were the first fluorinated surfactants to receive considerable attention, significant research has been carried out on PFCAs and PFSAs with shorter and longer chain lengths as well as a recent explosion of research in precursors and newer PFC classes that have been discovered, including perfluoroalkyl-sulfonamides, -ester phosphates, -phosphonates, -ethoxylates, -acrylates, -amino acids, -sulfonamide phosphates, -thioacids, and thioamidosulfonates as well as a new cyclic PFC that has been recently reported.

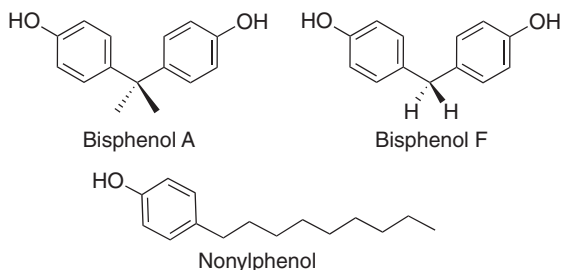
9.3 Plasticizers

9.3.1 Bisphenol A (BPA)

BPA (see Figure 9.1) is one of the top 50 industrial chemicals in production worldwide that are broadly used in the industry as plasticizers, and an important intermediate in the production of the following resins and polymers: polycarbonate, epoxy, polysulfone, polyacrylate, polyetherimide, unsaturated polyester, and phenolic [45]. Although of lesser importance, other uses have been reported, for example as an antioxidant in polyvinyl chloride (PVC) production, FRs, and other speciality products [46]. Final products include adhesives, protective coatings, powder paints, automotive lenses, protective window glazing, building materials, compact disks, optical lenses, thermal printing paper used for receipts, paper coatings, thermal and some dental fillings, sealants, as a developer in dyes, and for the encapsulation of electrical and electronic parts. A wide variety of food-contact materials stand out among their uses, mainly derived from polycarbonates and epoxy resins [47].

The structure of BPA is determined from the reaction of phenol with acetone. Phenol is condensed with acetone under low pH and high temperature conditions in the presence of catalysts. Crude BPA is then purified by distillation. The

Figure 9.1 Structure of nonylphenol and bisphenol A and F.



2 <https://www.epa.gov/ccl/chemical-contaminants-ccl-4>.

3 <http://water.epa.gov/lawsregs/rulesregs/sdwa/ucmr/ucmr3>.

molten purified product is filtered and dried. The dried BPA forms prills, flakes, or crystals. The main market for BPA is the production of polycarbonate with the second largest outlet being epoxy resins. Its volume of use is comparable to that of all phthalates together [48].

While BPA is molten at elevated temperatures during manufacturing (m.p. = 150–155 °C), releases to the environment are generally dissolved in water or are in the form of particulates. BPA has a reported water solubility of 120–300 mg L⁻¹ [49]. The USEPA [50] cites an unlisted reference that states that BPA has greater solubility at alkaline pH values due to its dissociation constants, pK_a 9.6–10.2 [51].

Numerous analytical methods have been developed for the determination of BPA in foodstuffs and urine samples [52, 53]. Sample clean-up is a major step in the determination of traces of BPA in complex matrices such as food and urine. It is commonly necessary to remove interfering matrix compounds to increase selectivity and to enrich BPA to lower the detection limit. Treatment of biological samples with glucuronidase and/or sulfatase enzyme during sample preparation prior to instrumental analysis is very common in order to cleave conjugate species and assess total concentration [54].

Similarly to BPA, bisphenol F (BPF) (see Figure 9.1) can be used in the production of epoxy resins and polycarbonates for lining large food containers and water pipes. Coatings can also be made from mixtures of BPA- and BPF-based resins. As with BPA, release into the environment is possible during manufacturing and by leaching from final products. Due to its chemical characteristics (log K_{ow} = 3.06; water solubility = 360 mg L⁻¹), the distribution and fate of BPF should be comparable to that of BPA.

9.3.1.1 BPA in the environment

Releases of BPA into the environment occur mainly via wastewater from industrial plants producing plastic products and from landfill sites. In 1993, an estimated 109 t or 0.017% of the 640,000 t BPA produced were reported as released to air and surface water or wastewater-treatment plants, with an additional 0.085% recycled, landfilled, or incinerated.

Because of its prolific use, BPA is ubiquitous in the environment [55]. Despite its proved degradation potential and its moderate hydrophobicity (log K_{ow} 3.32) and water solubility (120 mg L⁻¹), it is regularly detected in aquatic ecosystems, and consequently in groundwater. The extensive use of BPA-based polymers, with ester bonds subject to hydrolysis and non-polymerized monomer residues, has led to widespread environmental contamination.

BPA concentrations in the ranges of 5–320 ng L⁻¹ in river waters [56, 57], 20–700 ng L⁻¹ in sewage effluents [56, 57], 2–208 ng m⁻³ in air [58], 0.2–199 ng g⁻¹ in dust [58], and 0.1–384 ng g⁻¹ in foodstuffs [59] have been reported. BPA was detected in 40% of groundwater bodies identified as drinking-water sources investigated in Europe [60]. Conversely, it was found in only 3% of the samples analyzed in North America [60]. However, BPA concentrations were higher in North America than in Europe (maximum concentrations 6.4 µg L⁻¹ vs. 2.3 µg L⁻¹) [60]. BPA concentrations in a similar range, that is, between 0.1 and 5.6 µg L⁻¹, were measured in urban groundwater in two

German cities [61]. Concentrations of BPA up to 61 ng L^{-1} were determined in groundwater used for irrigation in China [62].

A total of 116 surface-water samples, 35 sediments from rivers, lakes, and channels, 39 sewage effluents, and 38 sewage sludges were collected and analyzed in Germany by Fromme *et al.* [63]. Furthermore, 10 liquid manure, 2 waste-dump, and two compost-runoff water samples were also analyzed. BPA measurements showed low concentrations from 0.0005 to $0.41 \text{ } \mu\text{g L}^{-1}$ in surface water, 0.018 to $0.702 \text{ } \mu\text{g L}^{-1}$ in sewage effluents, 0.01 to 0.19 mg kg^{-1} in sediments, and 0.004 to 1.363 mg kg^{-1} dw in sewage sludge. Measured concentrations of BPF were clearly lower than BPA in all environmental media [63]. BPA was also frequently detected in landfill leachates [64]. Thus, it is not surprising to find this compound in groundwater in the vicinity of landfill sites, as reported by Stuart *et al.* [65]. Up to $43 \text{ } \mu\text{g L}^{-1}$ of BPA were found in groundwater from the Southern England Chalk formation [65].

9.3.1.2 Toxicology and regulation of bisphenol A (BPA)

BPA is biodegraded during activated sludge-treatment processes [66], and therefore concentrations of BPA are expected to be low [66]. It was not detected in any surface waters, and was detected only in the influents of four STPs at 0.06 – $1.51 \text{ } \mu\text{g L}^{-1}$, and never at levels higher than $2 \text{ } \mu\text{g L}^{-1}$ (level linked to estrogenic activity) [55].

Its presence in food is of special concern since it constitutes the primary route of human exposure [47, 58]. In 1993, BPA was found to be released from polycarbonate flasks during autoclaving [55]. Since that time, several works have reported leakage of traces of BPA from polycarbonate containers [67–69] and epoxy linings into food [70–75].

BPA is a man-made alkyl phenol, well known in the scientific world as the xenoestrogen compound [76]. Due to the use of BPA in the manufacture of products used in many applications, it has been reported that human exposure to BPA may be widespread and that such exposure may reach high levels [50, 77, 78]. The widespread human exposure to BPA has been highlighted by its concentration levels in human fluids and tissues [78]. Concentrations in blood and urine were on average in the 0.3 – $4.4 \text{ } \mu\text{g L}^{-1}$ and 0.47 – $9.5 \text{ } \mu\text{g L}^{-1}$ ranges with a detection rate above 90% in most of the studies. Due to the widespread use of BPA-based polymers, BPA was detectable in 95% of urine samples collected from 395 US citizens [79]. In a further study by the same research group, BPA was detected in 92.6% of 2517 participants [80]. The scientific panel on food additives, flavorings, processing aids, and materials in contact with food of the EU has reported estimates of potential dietary exposure of 13, 5.3, and $1.5 \text{ } \mu\text{g kg}^{-1} \text{ d}^{-1}$ in 6- to 12-month-old breastfed infants, young children, and adults, respectively [47].

As an xenoestrogen compound, BPA, presents multiple modes of endocrine disruption activity; with the most emphasized being the binding to the α - and β -estrogen receptors and acting competitively toward natural hormones (e.g., E2). This estrogenic activity of BPA was first reported in 1993 [55]. The affinity of BPA for estrogen receptors is 10,000- to 100,000-fold weaker than that of E2, and therefore it has been considered as a very weak environmental estrogen. However, a large number of recent *in vitro* studies have shown that the effects

of BPA are mediated by both genomic and nongenomic estrogen-response mechanisms, with the disruption of the cell function occurring at doses as low as 1 pM (0.23 ng L^{-1}) [50].

When the BPA enters the blood circulation of the human body, biotransformation follows. At this point, the compounds are subject to glucuronidation and sulfation, localized mainly in the liver. Since they are converted to a large extent into glucuronides and sulfates, their potential estrogenicity is deactivated. Then, the conjugates are rapidly cleared away from blood through the kidneys and end up in urine for excretion [81]. Due to biotransformation and rapid clearance, only low levels (trace levels) of the analytes are likely to be detected in blood after a specified time period has elapsed from exposure. For instance, BPA reportedly has an elimination half-life of less than about 6 h in the human body [82].

Since 2007, a number of very extensive reviews have been published for human-exposure assessment and epidemiology studies on BPA [52, 78]. Diamanti-Kandarakis *et al.* [83] stated that clinical observations and epidemiological studies showed correlation between BPA and effects on the human reproductive system, breast and prostate cancer, thyroid, and metabolic syndromes such as obesity. Vandenberg *et al.* [84] cited more than 80 previous studies on BPA since 2000.

BPA is neither genotoxic nor carcinogenic and the guideline conformed to repeated dose toxicity studies, including studies on reproductive and developmental toxicity covering a wide dose range, which showed adverse effects only at doses $N_{50} \text{ mg kg}^{-1} \text{ d}^{-1}$ [85, 86].

Related to survival is a growth and development parameter ranging from 16 to 1280 mg L^{-1} . This concentration range markedly exceeds the measured concentrations in North American and European fresh waters (ranging from 0.081 to 0.47 mg L^{-1} and 0.01 to 0.05 mg L^{-1} , respectively) [87]. The EFSA, the WHO and the FAO declared that the actual effects of BPA on human health need to be validated by further research. The lack of scientific evidence of its toxicity at the current exposure levels and major methodological flaws were the main reasons for their declaration [88].

The EU banned the use of BPA in plastic infant-feeding bottles, making a landmark move to safeguard the health of infants and the general population [89].

9.3.2 Phthalates

Phthalate esters (PAEs) are widely used industrial chemicals that have been in use for more than 40 years, and constitute the main group of plasticizer agents [48], serving as important additives which impart flexibility in PVC resins. Phthalate esters are also used to varying degrees in other resins such as polyvinyl acetates, cellulose, and polyurethanes. The stability, fluidity, and low volatility of higher-molecular-weight phthalate esters make them suitable as plasticizers.

Most of the mid- to high-molecular-weight phthalate esters are used in the manufacture of PVC, while di-*n*-butyl phthalate is used in epoxy resins, cellulose esters, and specialized adhesive formulations. Dimethyl and diethyl phthalate esters are typically used in cellulose ester-based plastics, such as cellulose acetate and butyrate. Therefore, many consumer products contain specific members

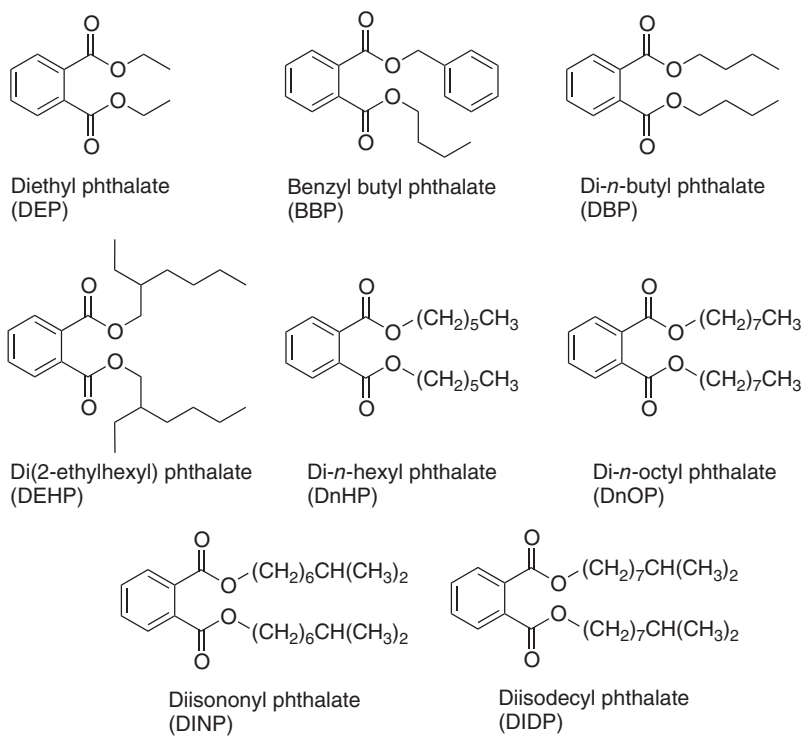


Figure 9.2 Structure of most common phthalates.

of this family of chemicals, including building materials, household furnishings, transportation, clothing, medical products, cosmetics, PCs, nutritional supplements, medical devices, dentures, children's toys, glow sticks, modeling clay, automobiles, lubricants, waxes, cleaning materials, insecticides, insect repellents, and to a limited extent in food (packaging) (see Figure 9.2 and Table 9.3) [90].

DEHP is one of the most widespread phthalate plasticizers, used in numerous consumer products, commodities, and building materials. Additionally, DEHP is still used as a plasticizer in medical products. While in earlier years DEHP was the predominantly used plasticizer with a production volume of 3–4 millions t worldwide [92], industrial production and use have decreased in recent years. Further, other phthalates such as DEP, DBP, BBP, and DnOP are widely used.

Review of the physicochemical properties of phthalate ester is a key step in understanding their activity and fate in the environment. A number of the remarkable physicochemical properties of phthalate esters are listed in Table 9.4.

Common commercial phthalate esters are liquids at ambient temperatures (see Table 9.4). Nearly all have a melting point (m.p.) below $-25\text{ }^{\circ}\text{C}$. Exceptions are DMP, DUP, and 610P with m.p. of $5.5\text{ }^{\circ}\text{C}$, $-9\text{ }^{\circ}\text{C}$, and $-4\text{ }^{\circ}\text{C}$, respectively. Phthalate esters have a boiling point (b.p.) varying from about $230\text{ }^{\circ}\text{C}$ to $486\text{ }^{\circ}\text{C}$. Higher-molecular-weight phthalate esters have a b.p. that must be determined at reduced pressure to prevent thermal decomposition. The low m.p. and high

Table 9.3 Use of phthalates (according to risk assessment of NTP CERHR, modified).^{a)}

	Use
Diethyl phthalate (DEP)	PCPs, cosmetics
Butyl benzyl phthalate (BBP)	Vinyl tiles, food conveyor belts, artificial leather, automotive trim, traffic cones
Disinfection by-product (DBP)	PVC plastics, latex adhesives, cosmetics, PCPs, cellulose plastics, solvent for dyes
DEHP	Building products (wallpaper, wire, and cable insulation), car products (vinyl upholstery, car seats), clothing (footwear, raincoats), food packaging, children's products (toys, grip bumpers), medical devices
Di- <i>n</i> -hexyl phthalate (DnHP)	Dipmolded products, such as tool handles, dish-washer baskets, flooring, vinyl gloves, flea collars, conveyer belts used in food processing
Di- <i>n</i> -octyl phthalate (DnOP)	In mixtures C ₆ – C ₁₀ phthalates: garden hoses, pool liners, flooring tiles, tarps Seam cements, bottle cap liners, conveyor belts (indirect food additive!)
Di- <i>iso</i> -nonyl phthalate (DINP)	Garden hoses, pool liners, flooring tiles, tarps, toys
Di- <i>iso</i> -decyl phthalate (DIDP)	PVC plastics, covering on wires and cables, artificial leather, toys, carpet backing, pool liners

a) Data taken from Ref. [91].

b.p. of these phthalate esters contribute to their usefulness as plasticizers, heat transfer fluids, and carders.

Water solubility is an extremely important property that influences the biodegradation and bioaccumulation potential of a chemical, as well as its aquatic toxicity. Water solubility is also a determining factor that controls the environmental distribution of chemicals. Reported aqueous solubilities of phthalate esters are summarized in Table 9.4. Results show a declining trend in water solubility with increased carbon number of the alcohol moiety for the lower-molecular-weight phthalates through DHP.

9.3.2.1 Phthalates in the environment

These compounds are produced and used in high volumes worldwide, and therefore they are continuously released into the environment. These esters have meanwhile been found in all types of environmental and many biological samples. The sorption of phthalate esters to soil, sediment, or suspended solids is partially governed by the relative hydrophobicity of the chemical. Such hydrophobic chemicals adsorb principally to the organic matter associated with the solid. Adsorption is generally measured by shake-flask techniques in which a solid, water, and test chemical are agitated in a closed system.

As the phthalate plasticizers are not chemically bound to PVC, they can enter the environment through losses during manufacturing processes and by leaching from final products, migration, or evaporation into indoor air and atmosphere, foodstuff, and other materials. Although these esters have since been found in all types of environmental and many biological samples, they are also frequently

Table 9.4 Physicochemical properties for the most common phthalate esters.^{a)}

Phthalate ester	M.p. (°C)	Specific gravity	Solubility (mg L ⁻¹)	Log K_{ow}
Di-(<i>n</i> -hexyl, <i>n</i> -octyl, <i>n</i> -decyl) phthalate (610P)	−4	0.970	0.9 ^{b)}	8.17 ^{a)}
BBP	−35	1.111	2.69 ^{b)}	4.77 ^{a)}
Butyl 2-ethylhexyl phthalate (BOP)	−37		<1.0 ^{b)}	5.64 ^{a)}
Di-(heptyl, nonyl, undecyl) phthalate (D711P)	<−50	0.970	<1.0 ^{b)}	8.60 ^{a)}
Diallyl phthalate (DAP)			182 ^{c)}	3.11 ^{a)}
DEHP	−47	0.986	0.27–0.36 ^{d)}	7.73 ^{a)}
DEP	−40	1.118	1080 ^{b)}	2.42 ^{e)}
Di- <i>iso</i> -hexyl phthalate (DHP)	−27.4	1.011	0.24 ^{b)}	6.00 ^{a)}
Di- <i>iso</i> -butyl phthalate (DIBP)	−58	1.050	20.3 ^{c)}	4.27 ^{a)}
DIDP	−46	0.961	1.19 ^{b)}	9.46 ^{a)}
DINP	−48	0.970	0.2 ^{b)}	8.60 ^{a)}
Di- <i>iso</i> -octyl phthalate (DIOP)	−46	0.986	0.09 ^{b)}	7.73 ^{a)}
Dimethyl phthalate (DMP)	5.5	1.192	4000 ^{b)}	1.60 ^{e)}
Di- <i>n</i> -butyl phthalate (DnBP)	−35	1.042	8.7–9.6 ^{d)}	4.50 ^{e)}
DnOP	−25	0.978	0.02 ^{d)}	8.18 ^{e)}
Di- <i>n</i> -propyl phthalate (DPP)			108 ^{c)}	3.40 ^{a)}
Ditridecyl phthalate (DTDP)	−37	0.953	<0.3 ^{b)}	12.06 ^{a)}
Diundecyl phthalate (DUP)	−9	0.960	1.1 ^{b)}	10.33 ^{a)}

a) Data taken from Ref. [93].

b) Data taken from Ref. [94].

c) Data taken from Ref. [95].

d) Data taken from Ref. [96].

e) Data taken from Ref. [97].

found in industrial wastewaters. The fate and activity of PAEs in the environment is greatly influenced by the alkyl chain length. Thus, their degradation rate appears to slow down at greater alkyl chain lengths because of the corresponding increase in log K_{ow} (which ranges from 1.46 to 13.1), indicating greater lipophilicity and less solubility [63]. Phthalates have low water solubility (3 $\mu\text{g L}^{-1}$) [63] and, when released into the aquatic environment, they tend to adsorb strongly to suspended particles and sediments [2]. As a consequence, DEHP and DEP constitute the most ubiquitous phthalates found in wastewaters, which correlates with their widespread use [98]. Thirty years ago, the release of phthalate esters into the environment during manufacture, use, and disposal was reviewed [92, 99].

In the late 1990s, several phthalates⁴ were measured by Fromme *et al.* [63] in various environmental compartments seeking a better understanding of exposure to these compounds in different environments. Their results were similar to those obtained from sediment examinations between 1985 and 1995 described in the literature [63].

4 BBP, DBP and DEHP.

DEHP dominated the phthalate concentrations, which ranged from 0.33 to 97.8 $\mu\text{g L}^{-1}$ (surface water), 1.74 to 182 $\mu\text{g L}^{-1}$ (sewage effluents), 27.9 to 154 mg kg^{-1} dw (sewage sludge), and 0.21 to 8.44 mg kg^{-1} (sediment). DBP was found only in minor concentrations and BBP, only in a few samples in low amounts. Very high concentrations of BPA and phthalates were confirmed in waste-dump water and compost-water samples as well as in the liquid-manure samples. The results for DEHP and DBP in samples of surface water, sediment, sewage water, and sewage sludge samples showed, particularly in the surface-water samples, large variations of over two orders of magnitude. Out of 115 surface water and 35 sediment samples, only one from each group lay below the determination limit (for DEHP and DBP). Surface water concentrations were from 0.33 to 97.8 $\mu\text{g L}^{-1}$ (median: 2.27 $\mu\text{g L}^{-1}$) for DEHP and from 0.12 to 8.80 $\mu\text{g L}^{-1}$ (median: 0.50 $\mu\text{g L}^{-1}$) for DBP. Concentrations in sediment were from 0.21 to 8.44 mg kg^{-1} dw (median: 0.70 mg kg^{-1} dw) for DEHP and 0.06 to 2.08 mg kg^{-1} dw (median: 0.45 mg kg^{-1} dw) for DBP [63].

Germain and Langlois [100] collected surface-water samples from the St. Lawrence River. Both dissolved phthalate ester and phthalate ester bound to suspended particulate matter (SPM) were analyzed. The SPM concentration was estimated to be 3.0 mg L^{-1} . About 14% of the total DnBP concentration was sorbed to SPM and 86% was dissolved.

DEHP has been also detected in cave streams in the United States [101] and in groundwater used as a drinking-water source in Mexico City (19–232 ng L^{-1}) [102]. Elevated concentrations of DEHP (46 $\mu\text{g L}^{-1}$) and other phthalates, that is, DEP (1.5 $\mu\text{g L}^{-1}$), and DMP (380 ng L^{-1}), were present in the groundwater from the Chalk (UK) [65]. DEHP and DBP were occasionally above 1 $\mu\text{g L}^{-1}$ in groundwater intended for drinking water in China [103].

Phthalate esters are susceptible to hydrolysis, although at slow rates. The products of hydrolysis are an acid and an alcohol. Phthalate esters can go through two hydrolytic steps, producing first the mono-ester and one free alcohol moiety and a second hydrolytic step producing phthalic acid and a second alcohol. Ester hydrolysis may be either acid or base catalyzed, with, in some instances, metal ions, anions, or organic materials serving as catalysts. Acid hydrolysis of phthalate esters is possible, but is estimated at four orders of magnitude slower than alkaline hydrolysis rate constants [104].

Aqueous photolysis occurs through absorption of UV light from sunlight in the 290–400 nm region. Photolysis can be mediated via either direct or indirect mechanisms. The mechanism of photolysis may be either through direct absorption of UV radiation by the chemical or by absorption of UV radiation with the formation of activated species such as singlet oxygen or hydroxyl radicals that react with phthalate esters.

Biodegradation is a critical process affecting the environmental fate of phthalate esters (see Figure 9.3). Microbes from diverse habitats have been shown to degrade phthalate esters and resulting intermediates. Representatives from both aerobic and some anaerobic environments include gram-positive and gram-negative bacteria and actinomycetes. Although some individual microbes are capable of completely mineralizing phthalate esters, more efficient metabolism appears to result from mixed microbial populations, typically found in the environment [105].

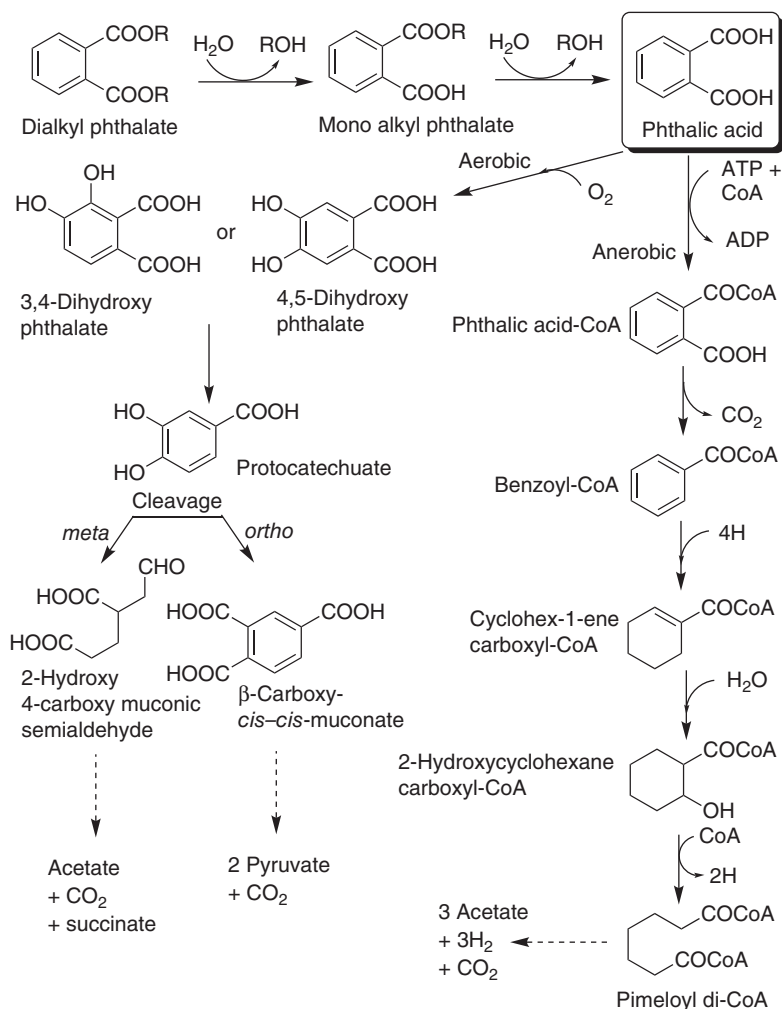


Figure 9.3 General biodegradation pathway for phthalate esters in the environment. Data taken from Ref. [90]

9.3.2.2 Toxicology and regulation of phthalates

Consumer products containing phthalates can result in human exposure through direct contact and use, indirectly through medical procedures, diet, and/or mouthing of DEHP-containing objects. Risk assessments on phthalates have been made by different expert panels in Europe and America [106, 107].⁵

Phthalates exhibit low acute toxicity with LD_{50} values of 1–30 g kg^{-1} bw or with even higher concentrations. Certain phthalates have also shown estrogenic activity [2]. DEHP is classified as a probable carcinogen by the National Toxicology Program.

5 Agency for Toxic Substances & Disease Registry (ATSDR). Toxicological Profiles. Information About Contaminants Found at Hazardous Waste Sites. <https://www.atsdr.cdc.gov/ToxProfiles>.

DEHP is considered a priority substance in the EU [7] and its presence in drinking water is also regulated by the USEPA (see Table 9.2) [6].

9.3.3 *N*-Butylbenzenesulfonamide (NBBSA)

N-butylbenzenesulfonamide (NBBSA) is used widely as a plasticizer in polyacetals, polycarbonates, and polysulfones (see Figure 9.4), and is also used in nylon-11 and nylon-12. Additionally, it is used in the production of films, transparent coatings, and plastic resins [108]. NBBSA allows for easier machining and removal of plastics from molds, produces a better finish, and imparts heat stability. In addition to its plasticizing ability, NBBSA possesses antifungal properties [109]. It was previously described as a starting reagent for the synthesis of a proposed sulfonyl carbamate herbicide [110].

NBBSA is produced by reacting *N*-butylamine with benzenesulfonyl chloride. The aggregate US production volume of NBBSA ranged from 450 to <4500 t in 2006.⁶

9.3.3.1 NBBSA in the Environment

Studies of the presence of NBBSA in environmental media date back over 40 years. For example, NBBSA was identified as a contaminant of groundwater and drinking water in Italy in 1991 [111]. Additionally, NBBSA was detected in the Delaware river in 1977, where concentrations ranged from trace amounts to 0.6 ppb [112]. Studies have been conducted in the United States as well as in England, Italy, the Netherlands, Germany, Sweden, and Japan.

The sulfonamide plasticizer NBBSA was one of the most ubiquitous and abundant ($240 \mu\text{g L}^{-1}$) synthetic organic chemicals present in UK groundwater [65]. Two other sulfonamide plasticizers, namely *N*-ethyl-2-methylbenzenesulfonamide and *N*-ethyl-4-methylbenzenesulfonamide, were also found in these groundwater samples (see Figure 9.4). Despite this, *N*-ethyl-2-methylbenzenesulfonamide was not ubiquitous in groundwater, where it was found at concentrations up to $561 \mu\text{g L}^{-1}$ [65].

NBBSA was found in all pre-tertiary treatment water samples and was present at the highest concentration (≈ 1 to $16.3 \mu\text{g L}^{-1}$) compared to the other substances detected. It was also present in most of the post-tertiary treatment water samples. However, concentrations were dependent on the treatment method used.

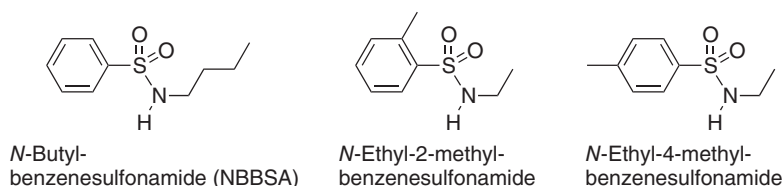


Figure 9.4 Chemical structure of *N*-alkylmethylbenzenesulfonamides

⁶ USEPA. 2010. Non-confidential 2006 IUR Records by Chemical, including Manufacturing, Processing and Use Information Office of Pollution, Prevention and Toxics. Benzenesulfonamide, *N*-butyl-. <http://cfpub.epa.gov/iursearch/index.cfm?s=chem>.

NBBSA was also present in groundwater and surface water samples but below the detection level [113].

Runoff from agricultural fields irrigated with treated wastewater and/or effluent-dominated stream water revealed the presence of NBBSA ($0.35\text{--}2\ \mu\text{g L}^{-1}$) [114, 115].

NBBSA was also detected in samples taken from eight locations in the Rhine River in Germany in 2001, with levels in the $92\text{--}190\ \text{ng L}^{-1}$ range [116]. Leachate samples obtained in 1994 from three sites in Sweden had concentrations of NBBSA that ranged from 709 to $5300\ \text{ng L}^{-1}$ [117].

N-Ethyl-4-methyl-benzenesulfonamide was also detected in the $\mu\text{g L}^{-1}$ range ($38\ \mu\text{g L}^{-1}$) in an anoxic aquifer located downgradient of a former sewage farm, and comparatively low concentrations (up to $0.3\ \mu\text{g L}^{-1}$) were measured in river-bank filtrate [118].

9.4 Flame Retardants

FRs include a broad and diverse group of compounds used to prevent fires or at least to slow down the spread of a blaze. There are three main categories of chemical FRs: halogenated hydrocarbons, organophosphorus compounds, and inorganic products often based on metallic hydroxides [119]. Among the halogenated hydrocarbons, the group of the brominated flame retardants (BFRs) consist of different chemicals with a variety of physicochemical properties and uses.

Consumer products and construction materials are frequently treated with FRs to reduce their flammability. Historically, polybrominated diphenyl ethers (PBDEs) were used as the primary FRs in polyurethane foam and electronics. However, concern over the persistence, bioaccumulation, and toxicity of PBDEs led to regulatory actions and drastic reductions in their use in the mid-2000s. During the same period, the use of alternative FRs increased, allowing manufacturers to maintain compliance with fire-safety standards and regulations [120–122].

Alumina trihydrate, $\text{Al}(\text{OH})_3$, was the most widely used FR in the world in 2013, accounting for nearly one-third of global sales (see Figure 9.5). Phosphorus-based FRs, on the other hand, are making the fastest market gains among major product types. Other FRs, such as halogenated retardants, represented by bromine- and chlorine-based products, are being phased out across the globe due to their perceived environmental and human health risks. In 2011, 390,000 t of brominated FRs were sold. This represents 19.7% of the flame-retardants market.

9.5 Brominated Flame Retardants (BFRs)

BFRs have been used for many years in a variety of commercial products including children's sleepwear, foam cushions in chairs, computers, plastics, and electronics. The rationale for using brominated compounds as FRs is based on

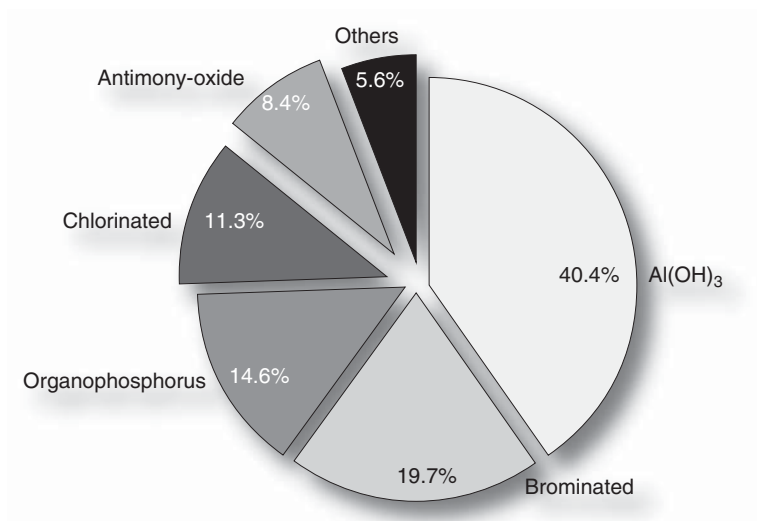


Figure 9.5 Total volume of flame-retardant world production.⁷

the ability of halogen atoms, generated from the thermal decomposition of the bromo organic compound, to chemically reduce and retard the combustion. BFRs work by releasing bromine-free radicals when heated, and these free radicals scavenge other free radicals that are part of the flame-propagation process. The use of these FRs is believed to have successfully reduced fire-related deaths, injuries, and property damage. However, there is concern because of their widespread presence in the environment and in human and wildlife samples as well as their presence in locations far from where they are produced or used.

The main BFRs are the polybrominated (i) neutral aromatic, (ii) neutral cycloaliphatic, (iii) phenolic, including neutral derivatives, (iv) aromatic carboxylic acid esters, and (v) tris-alkyl phosphate compounds.

The major individual groups of BFRs within these five classes are PBDEs, HBCDD, TBBPA and other brominated phenols, hexabromobenzene (HBB), decabromodiphenyl ethane (DBDPE), 1,2-bis(2,4,6-tribromophenoxy)ethane (BTBPE), bis(2-ethylhexyl) 2,4,6-tetrabromophthalate (bEH-TeBPht), and tris[3-bromo-2,2-bis(bromomethyl)propyl] phosphate (tBbBMPPrP) (see Figure 9.6) [123, 124].

Global production of brominated FRs⁸ is extremely high, estimated at 100,000–180,000 t yr⁻¹ range [125].

9.5.1 Polybrominated Diphenyl Ether (PBDE)

PBDE has been a popular ingredient in FRs since polybrominated biphenyls were banned about 30 years ago. Because many states and the federal government

⁷ Data taken from <https://www.flameretardants-online.com/flame-retardants/market>.

⁸ Including bromophenols, bromophenyl ethers, brominated phenyl esters, other bromoaromatic compounds, and brominated and chlorinated cyclic aliphatic compounds.

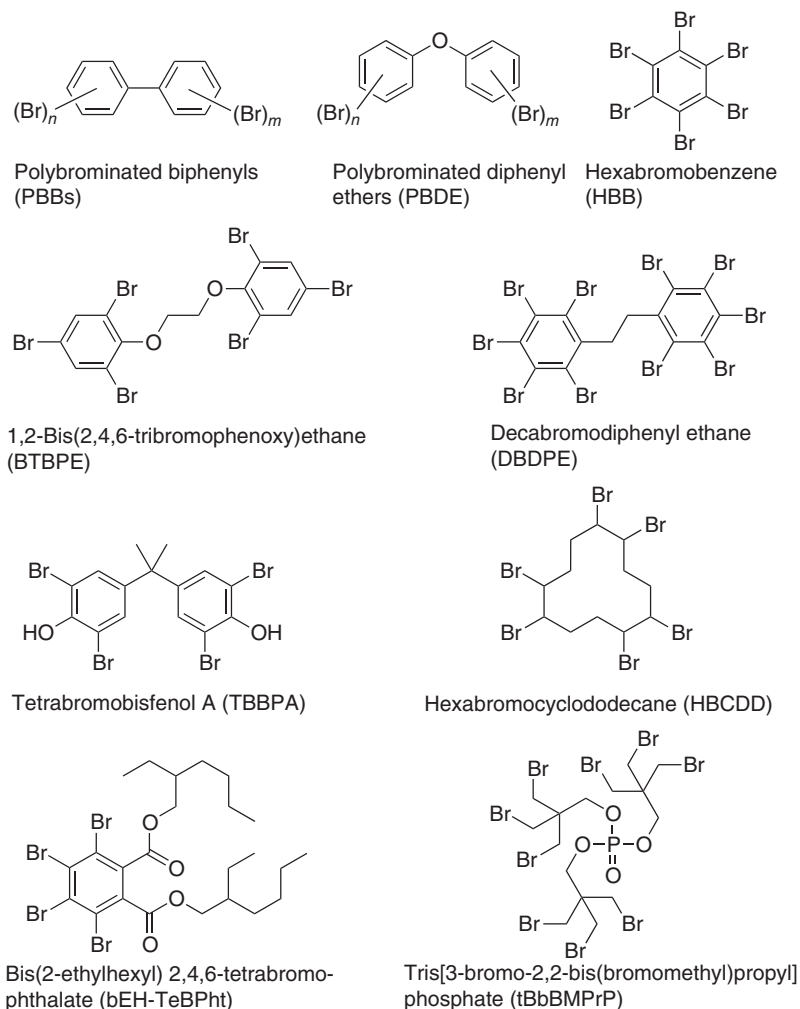


Figure 9.6 Structure of some polybrominated compounds.

now have regulations requiring most household products, such as mattresses and electronics, to be flame resistant, PBDE has become an important commercial substance. Factors favoring the use of PBDEs are therefore the high bromine content (which means good flame-retardant properties), thermal stability, and relatively low cost.

The general chemical formula of a PBDEs is $C_{12}H_{(9-0)}Br_{(1-10)}O$, with the sum of H and Br atoms always equal to 10. Structure formulas and nomenclature are given in Figure 9.6.⁹

The theoretical number of possible congeners is 209 and is divided into 10 congener groups (mono- to deca-BDEs, containing between 1 and 10 bromine

⁹ For convenience, the congeners are numbered from 1 to 209 using the same IUPAC scheme used for polychlorinated biphenyls.

Table 9.5 Nomenclature for PBDEs, chemical formula, and number of isomer congeners.

Homologs	Formula	No. of isomer congeners	Congeners
Mono-BDEs	$C_{12}H_9OBr$	3	BDE-1 to BDE-3
Di-BDEs	$C_{12}H_8OBr_2$	12	BDE-4 to BDE-15
Tri-BDEs	$C_{12}H_7OBr_3$	24	BDE-16 to BDE-39
Tetra-BDEs	$C_{12}H_6OBr_4$	42	BDE-40 to BDE-81
Penta-BDEs	$C_{12}H_5OBr_5$	46	BDE-82 to BDE-127
Hexa-BDEs	$C_{12}H_4OBr_6$	42	BDE-128 to BDE-169
Hepta-BDEs	$C_{12}H_3OBr_7$	24	BDE-170 to BDE-193
Octa-BDEs	$C_{12}H_2OBr_8$	12	BDE-194 to BDE-205
Nona-BDEs	$C_{12}HOBr_9$	3	BDE-206 to BDE-208
Deca-BDEs	$C_{12}OBr_{10}$	1	BDE-209

atoms). However, compounds with less than four bromine atoms are generally not found in commercial PBDEs products. Of these, only 23 congeners are of environmental significance PBDEs congeners are often numbered according to the IUPAC system originally designed for PCBs (see Table 9.5) [126].

PBDEs are commercially available as three products, two of which are mixtures of several congeners [123]. The so-called penta-BDE contains BDE-47, BDE-99, BDE-100, BDE-153, and BDE-154, at a ratio of about 9:12:2:1:1 [127]. The octa-BDE contains several hexa- to nona-BDE congeners, and the deca-BDE is almost entirely composed of BDE-209 [123]. Similar to most commercial chemical mixtures, the composition of these products varies with the manufacturer and with the year in which they were produced.

They are used as additive FRs at concentrations of 5–30% in many different polymers, resins, and substrates as well as in common plastics, including acrylonitrile, butadiene, styrene, and high-impact polystyrene. Additive FRs leach and escape from the finished polymer product more easily than do reactive FRs.

Examples of products containing FRs, especially PBDEs, include many components of electronic devices, for example, cabinets for and circuit boards in personal computers and television sets and various other products (electrical cables, switches, and capacitors), building materials, and textiles (see Figure 9.7). The technical deca BDEs have the widest industrial use. More details about the use of PBDEs in various resins or polymers and the applications of these PBDE containing resins are given in Table 9.6 [129].

PBDEs are used as FRs in a wide variety of commercial and household products, such as furniture, electronics, foam insulation, and building materials, which prevent them from burning easily. For example, polyurethane foam, which is widely used in upholstered furniture, is flammable unless it is treated with suitable FRs such as PBDEs. In fact, some polyurethane foam is treated with 10–30 wt% of PBDEs to make this material safe for home use [131]. PBDEs are used as FRs in plastics (concentration, 5–30%) and in textile coatings.

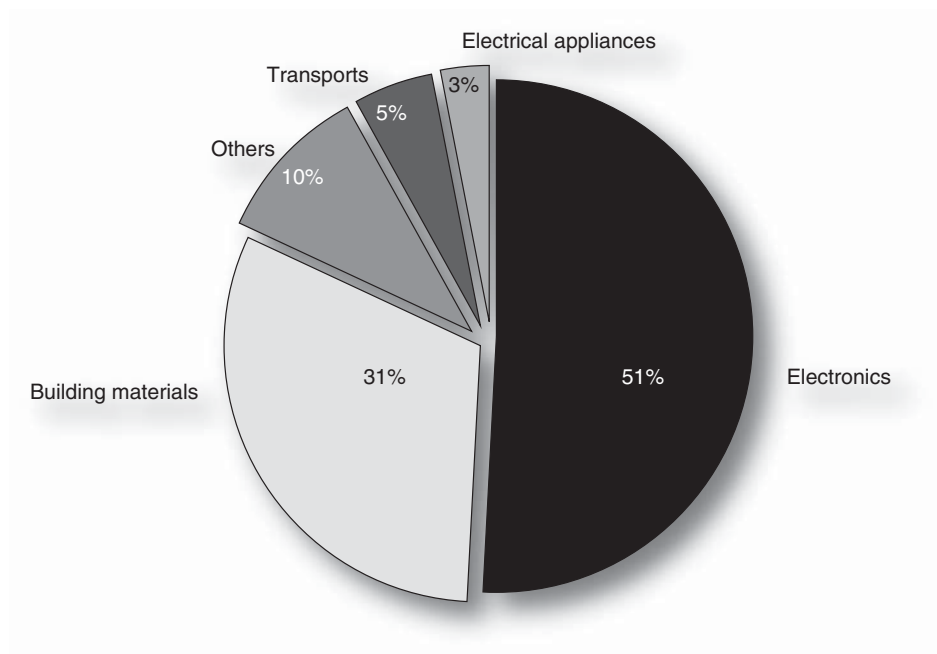


Figure 9.7 Relative amounts of FRs used in different sectors. Data taken from Ref. [128]

The global production figures have stayed at approximately the same levels for more than 10 yrs, but there has been a shift in use toward the higher brominated preparations. Consequently, the use of deca-BDE today is even more prevalent. During the 1990s, the commercial production or import of PBDEs (penta-, octa-, and deca-BDEs) in the United States was greater than 1500 t yr^{-1} during the 1990s [132].

Commercial PBDEs are synthesized by bromination of diphenyl ethers under conditions resulting in mixtures of brominated diphenyl ethers. Commercial products consist predominantly of penta-, octa-, and deca-bromodiphenyl ether mixtures, and the global PBDEs production is about $40,000 \text{ t yr}^{-1}$. Chemically, the pentabromo product is a mixture primarily of tetra and penta congeners, and the octabromo product consists mainly of hepta and octa congeners (see Table 9.7). Consequently, almost no data are available on mono-, di-, tri-, hexa-, and nona-BDEs. The number of different congeners found in each commercial product is relatively small. The composition of commercial brominated diphenyl ethers is given in Table 9.7.

Commercial PBDEs are quite resistant to physical, chemical, and biologic degradation. Boiling points of PBDEs are in the $310\text{--}425^\circ\text{C}$ range and their vapor pressure are low at room temperature (r.t.). PBDEs are lipophilic, and their solubility in water is low, especially for the higher brominated compounds. The $\log K_{ow}$ gave values in the 4.3–9.9 range. PBDEs are non-ionisable compounds and present low volatility [133]. Physicochemical properties are summarized in Table 9.8 [129].

Table 9.6 Use of penta- (PeBDE), octa- (OBDE), and deca-bromodiphenyl ethers (DeBDE) in resins, polymers, and substrates.^{a)}

Resins/polymers/substrates	DeBDE	OBDE	PeBDE
acrylonitrile butadiene styrene (ABS)	–	✓	–
Epoxy-resins	✓	–	–
Phenolic resins	✓	–	✓
PAN	✓	–	–
PA	✓	✓	–
PBT	✓	✓	–
PE/XPE	✓	–	–
PET	✓	–	–
PP	✓	–	–
PS, HIPS	✓	✓	–
PVC	✓	–	✓
PUR	–	–	✓
UPE	✓	–	✓
Rubber	✓	–	✓
Paints/lacquers	✓	–	✓
Textiles	✓	–	✓

a) Data taken from Ref. [130].

Despite their social benefits, PBDEs seem to be migrating from the products in which they are used and contaminating the environment and people. PBDEs are now ubiquitous; they can be found in air, water, fish, birds, marine mammals, and humans, and in many cases, the concentrations of these compounds prove to be increasing over time.

The presence of PBDEs in the environment has been reviewed [124, 129, 134–137], including a complete issue of *Environment International* [138]. Many of these reviews have been exhaustive in scope (including both chemistry and toxicology).

PBDEs are used as FRs in a wide range of products, and waste from these products is probably the main source of PBDEs in the environment. The waste is either incinerated as municipal waste or deposited in landfills. Although specific data are missing, incineration is thought to be a major route of release of PBDEs into the environment. No study on leaching of PBDEs from landfills is available, but PBDEs-containing products are widespread, and leaching may be an important long-term pathway of contamination. PBDEs are discharged into the environment through sewage, as indicated by analysis of sewage sludge from various countries. Volatilization of PBDEs into the surrounding air from electrical components and other products during their lifetime can also be significant. Apart from anthropogenic sources, PBDEs-related brominated compounds also appear to be formed by nature and have been detected in certain marine sponges [139].

Table 9.7 Composition of commercial PBDEs.^{a)}

Compounds	Commercial products			
	Tetra-BDE (%)	Penta-BDE (%)	Octa-BDE (%)	Deca-BDE (%)
Unknown	7.6			
Tri-BDE		0–1		
Tetra-BDE	41–41.7	24–38		
Penta-BDE	44.4–45	50–62		
Hexa-BDE	6–7	4–8	10–12	
Hepta-BDE			43–44	
Octa-BDE			31–35	
Nona-BDE			9–11	0.3–3
Deca-BDE			0–1	97–98

a) Data taken from Ref. [130].

Table 9.8 Physicochemical properties of some PBDEs.^{a)}

Compounds	Formula	M.p. (°C)	Vapor pressure (Pa)	Log K_{ow}
BDE-47	$C_{12}H_6OBr_4$	82.6–83	$2.7\text{--}3.3 \times 10^{-4}$	5.9–6.2
Penta-BDE	$C_{12}H_5OBr_5$	97–98 (BDE-100)	$2.9\text{--}7.3 \times 10^{-5}$	6.5–7.0
Octa-BDE	$C_{12}H_2OBr_8$	~200	$1.2\text{--}2.7 \times 10^{-7}$	8.4–8.9
Deca-BDE	$C_{12}OBr_{10}$	290–306	$<1 \times 10^{-4}$	10

a) Data taken from Ref. [130].

Perhaps as a result of their lipophilicity, these compounds are recalcitrant, bioaccumulative in animals and humans, and environmentally persistent [140]. Several works have been published regarding seafood contamination by PBDEs [124, 141–143]. BDE-47 is commonly the most concentrated pollutant in seafood, reaching up to 81,800 ng g⁻¹ lipid weight (lw) in mud carp as reported by Wu *et al.* [144].

In 2004, the major US manufacturer of PBDE-based FRs (Great Lakes Chemical) voluntarily stopped producing the penta- and octa-BDEs.

Due to their low water solubility ($<0.13 \mu\text{g L}^{-1}$) and high log K_{ow} values (<10) [145], PBDEs are likely to partition into the environmental solid matrices. However, these brominated FRs have also been detected in groundwater. For instance, PBDEs were present in a fractured bedrock aquifer in Canada at higher concentrations than in surface-water bodies [146]. Total PBDE concentrations in this aquifer reached up to 94 ng L⁻¹ [146]. These compounds were also present in a cave stream system in the United States [101]. Overall, the main contributors to total PBDE levels in groundwater were PBDE-209 (deca-BDE), PBDE-47 (a tetra-BDE), and PBDE-99 (a penta-BDE) [101, 146].

One particularly groundbreaking study was a new discovery of co-leaching of decabromodiphenyl ether (BDE-209) with antimony from PET plastic bottles into bottled water [147]. BDE-209 is used as a FR in the preparation of polyethylene terephthalate (PET) and polycarbonate (PC) plastics, and Andra *et al.* [147] published the first report of PBDEs in bottled water. Plastic bottles included PET, PC, high-density polyethylene (HDPE), and polystyrene (PS).

These and other data clearly indicate that the environment and the inhabitants of North America are far more contaminated with PBDEs when compared to Europe and that these PBDEs levels have doubled every 4–6 yr. Analyses of the relative distributions of the most abundant PBDE congeners indicated that these patterns cannot yet be used to assign sources to these pollutants [148].

For their analysis, extraction methods normally used for environmental (biological and sediment) samples are batch extraction or soxhlet extraction. Different methods of cleanup are used depending on the nature of the other compounds analyzed and the type of analytic method applied. Among these procedures are sulfuric acid cleanup and different types of column separations.¹⁰ Recently, supercritical fluid extraction has also been described [149]. GC analysis is normally performed in capillary columns with methyl or methyl plus 5% phenyl packing substrates. Detection is made on an electron capture detector.¹¹ The high-brominated diphenyl ethers with longer retention times are analyzed using a shorter GC column.

Details about the toxicity of PBDEs were given by Darnerud *et al.* [129]. They have been known to cause tumors, neurodevelopmental toxicity, endocrine disruption, and thyroid hormone imbalance [140]. They affect the thyroid gland, may interfere with other natural hormones, trigger reproductive problems, and cause developmental and neurological damage. Studies indicate near universal exposure to PBDEs among the general population [150, 151]. Characteristic end points of animal toxicity are hepatotoxicity, embryotoxicity, and thyroid effects as well as maternal toxicity during gestation.

In 2004, the EU banned the use of the penta- and octa-BDEs and later, in 2008, banned deca-BDEs. As defined in the European Commission Decision 2005/717/EC [152], deca-BDE can no longer be used in electronics and electrical applications in Europe since July 2008, and a maximum level of 0.1% of total PBDEs shall be tolerated [152, 153]. In 2009, the Commission Regulation No. 552/2009 updated the restriction conditions for Penta-BDE and Octa-BDE, set in ANNEX XVII of this Regulation [154]. As a consequence, these cannot be placed on the market or used as substances, in mixtures or in articles, at concentrations higher than 0.1% by mass.

Consequently, the use of certain brominated FRs, such as PBB and tris(2,3-dibromopropyl) phosphate, in textiles has already been banned.

Tetra-, penta-, hexa-, and hepta-BDE are considered priority substances in the EU, and therefore, their occurrence in surface waters is regulated (see Table 9.2).

10 For example, silica gel, aluminum oxide, and gel-permeation chromatography.

11 Mass spectrometry-electron impact ionization or mass spectrometry-electron capture negative ionization.

Priority PBDEs concentrations were not affected after MAR via injection of treated wastewater [155].

9.5.2 Tetrabromobisphenol A (TBBPA)

TBBPA is the highest-volume brominated flame retardant (BFR) in production today, and is used as a reactive FR in epoxy, vinyl esters, and polycarbonate resins, being covalently bound into the polymer backbone. The main application of TBBPA is as a reactive FR in laminates (e.g., epoxy resins) for an estimated 90% of printed wiring boards. Among all the different FRs that can be used in printed wiring boards, TBBPA is the most well-researched FR. In epoxy resins, the bromine content may be 20% by weight. TBBPA is also used as either reactive or additive intermediates in polymer manufacture such as ABS resins, high-impact polystyrene (HIPS) and phenolic resins, adhesives, paper, and textiles, and others. It is used to prepare fire-resistant polycarbonates by replacing some BPA. TBBPA is chemically bound in these applications and has no potential for emissions to the environment.

TBBPA is considered as an alternative additive FR to octabromodiphenyl ether in ABS. When used as an additive FR, it is generally used combined with a synergist such as antimony trioxide for maximum FR performance. As an additive FR, TBBPA may more or less readily leach out of the polymer matrix. Additive use accounts for approximately 10% of the total use of TBBPA.

TBBPA may also be used as a parent compound for the production of other commercial FRs, such as TBBPA-bis(2-hydroxyethyl ether) (TBBPA-bOHEE), TBBPA-bis(2,3-dibromopropyl)ether (TBBPA-bDiBPrE), TBBPA-bisallyl ether (TBBPA-bAE), TBBPA-bismethyl ether (TBBPA-bME), TBBPA-brominated epoxy oligomer, and TBBPA carbonate oligomers.

The derivatives are used mainly as FRs, usually in niche applications. The total amount of TBBPA derivatives used is less than the amount of TBBPA used (approximately 25% wb) [156]. The derivatives may be used as either reactive or additive intermediates in polymer manufacture.

The basic structure of TBBPA consists of two hydroxyphenyl rings linked by a carbon bridge with bromine substitution at the 3,3',5 and 5'-position (see Figure 9.8). There are several TBBPA derivatives, of which a number is commercially available as FRs: TBBPA-bis(2-hydroxyethyl) ether (TBBPA-bOHEE), TBBPA-bisallyl ether (TBBPA-bAE), TBBPA-bis(2,3-dibromopropyl ether) (TBBPA-bDiBPrE), and TBBPA-bis(glycidyl ether) (TBBPA-bGE). For other TBBPA derivatives, there is some uncertainty about their commercial use as FRs: TBBPA-bisacrylate (TBBPA-bAcr), TBBPA-bis-acetate (TBBPA-bOAc), and TBBPA-bis(2-hydroxyethyl)ether bisacrylate (TBBPA-bOHEE-bAcr). TBBPA derivatives that may potentially be used as BFRs are TBBPA-bismethyl ether (TBBPA-bME) and TBBPA-bispropanoate (TBBPA-bOPr). The structure of each of these derivatives is presented in Figure 9.8.

Detailed information on the physicochemical characteristics of TBBPA is given in the EU risk assessment document [157]. TBBPA is a colorless solid, although commercial samples appear yellowish. The m.p. is 180–184 °C and it is soluble

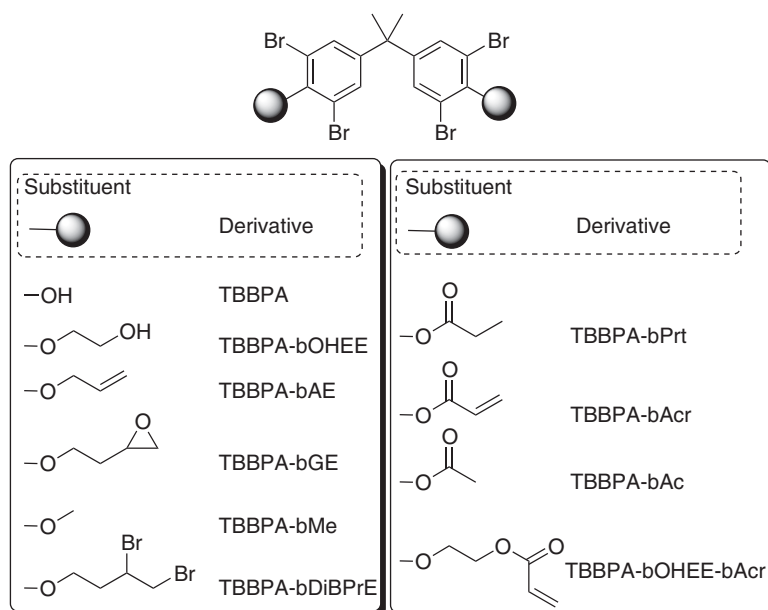


Figure 9.8 Structure of the most common TBBPA derivatives.

in methanol and ether. The two phenolic groups in TBBPA have been shown to have different pK_a values.

TBBPA is produced by the reaction of bromine with BPA, in the presence of various solvents. When methanol is used as the solvent, methyl bromide is formed as a by-product. The production process is largely conducted in closed systems. Bromination of BPA leads to the formation of primarily the tetrabrominated form of bisphenol A. Traces of isomeric TBBPA and tribromobisphenol A may be present in commercial TBBPA. Each of the TBBPA derivatives is produced as an individual chemical, and not as a mixture (see Figure 9.8).

Most commercial TBBPA products consist of a mixture that differs in the degree of bromination with the formula $C_{15}H_{16} - xBr_xO_2$ where $x = 1-4$. Its fire-retarding properties correlate with %Br.

The analytical method starts with the extraction of the TBBPA from the sample. Several methods for extraction of biological samples have been proposed in the literature as reviewed by Covaci *et al.* [158].

The polymer, as a result of excess TBBPA added during the production process of the polymer, will also contain a portion of unreacted TBBPA. As this unreacted TBBPA is not bound to the polymer, it represents a fraction that can easily leach out from the polymer matrix into the environment and subsequently result in exposure of animals and humans. Data from the analysis of TBBPA in 652 food samples were submitted to EFSA by four European countries (Ireland, Norway, Spain, and the United Kingdom), covering the 2003–2010 period. All analytical results were reported as less than the limit of quantification.

Occurrence data on TBBPA and its derivatives in seafood is scarce[[124], and references cited therein]. As determined under experimental conditions,

TBBPA undergoes photolysis [159] and oxidative transformations [160]. A number of transformation products, including debromination products, dibromohydroquinone, dibromo-isopropylphenol, and brominated alkylphenols have been detected. The anaerobic degradation of TBBPA was confirmed by Gerecke *et al.* [161]. TBBPA is not hydrolyzed and does not undergo substitution reactions. It is easily polymerized or copolymerized, due to the reactivity of the phenol groups. Toxicological studies with TBBPA have been carried out using different experimental designs with single or repeated administration during gestation, postnatally or in the adult stage. The main target is thyroid hormone homeostasis. TBBPA is not genotoxic, and there are no indications that TBBPA might be carcinogenic.

TBBPA has been shown *in vitro* to bind to estrogen hormone receptors at high concentrations [162] and cause other effects on hormone-sensitive parameters [163].

In 2006, the European Chemicals Bureau (ECB) published the risk assessment report on TBBPA [157]. For adults, no adverse health effects of potential concern were identified. No comparison of the intake estimate ($7.8 \times 10^{-5} \text{ mg kg}^{-1} \text{ d}^{-1} \text{ bw}$) and data from the toxicological studies was done. For infants, a no-observed-adverse-effect level (NOAEL) of $40 \text{ mg kg}^{-1} \text{ d}^{-1} \text{ bw}$ for nephrotoxicity in newborn rats [164] was used for risk characterization. No risk assessments have hitherto been presented for any of the TBBPA derivatives. However, to date none of the above-mentioned brominated phenols are regulated under any specific legislation for their use or production, without even any maximum tolerance levels in foodstuffs [124].

9.5.3 Polybrominated Biphenyls (PBBs)

The 209 possible polybrominated biphenyl (PBB) congeners, with the increasing degree of bromination, become more lipophilic compounds, thus achieving lower vapor pressures and lower water solubility. PBBs were produced until the mid-1980s, except deca-BB which was produced until 2000 [124].

According to the Directive 2002/95/EC, new electrical and electronic equipment put on the market after July 1, 2006 should not contain either PBBs or PBDE [153]. According to the Directive 2011/65/EC, PBBs were limited to 0.1% [165]. In 2010, during the Conference of the Parties of the Stockholm Convention, hexabromobiphenyl as well as all PBDEs were classified as a POP of strict elimination.¹² Despite not being currently manufactured, PBBs are still present in both biotic and abiotic samples, due to their environmental persistence. Few studies focused on their assessment in seafood [124].

9.5.4 Hexabromobenzene (HBB)

HBB is an emerging BFR that may undergo nucleophilic aromatic substitution with strong nucleophiles and reductive debromination under environmental

¹² Stockholm Convention on Persistent Organic Pollutants (SCPOP), 2012. Proposal to Amend Annex A to the Stockholm Convention to be discussed at the Sixth Meeting of the Conference of the Parties. Geneva, pp. 1–6.

conditions [166]. To date, HBB is not regulated in the EU under any specific legislation for their use or production [167], not even regarding maximum tolerance levels in foodstuffs.

9.5.5 Hexabromocyclododecane (HBCD)

HBCDs are established BFRs formed via the addition of bromine to 1,5,9-cyclododecatriene, consisting mainly of three stereoisomers (α -, β -, and γ -HBCD) substituted with six bromine atoms in the cyclododecane ring [133]. They can be effective alternatives for PBDEs in some applications.

Currently, all three main isomers are included in Annex XIV of the amended Regulation No. 1907/2006, which lists substances subject to authorization [167]. The Panel on Contaminants in the Food Chain (CONTAM Panel) concluded that current dietary exposure to HBCDs in the EU does not raise a health concern [168]. Several papers have reported the levels of total HBCD or their individual congeners in seafood [[124], and references cited therein].

9.5.6 Decabromodiphenyl Ethane (DBDPE)

DBDPE has a polybrominated character with lipid-soluble features and low volatility [169]. It was introduced in the mid-1980s, becoming commercially significant as an alternative to BDE-209. DBDPE is not regulated under any specific rules for use or production, not even regarding maximum tolerance levels in foodstuffs, although it has been detected in seafood [[124], and references therein].

9.5.7 1,2-Bis(2,4,6-Tribromophenoxy)ethane (BTBPE)

Similar to decabromodiphenyl ethane (DBDPE), 1,2-bis(2,4,6-tribromophenoxy) ethane (BTBPE) is a lipid-soluble contaminant of low volatility. BTBPE is an additive FR that has been produced since the mid-1970s. BTBPE has not been regulated, under any specific directives either for use or for production [[124], and references therein].

9.6 Polychlorinated Alkanes (C_{10} – C_{13})

Organohalogen compounds such as polychlorinated naphthalenes (PCNs), chlorinated paraffins (CPs), and polychlorinated biphenyls (PCBs) are well known environmental contaminants. These three classes of compounds are ubiquitous global pollutants that can be often found in different environmental compartments, although their use and production has been restricted (CPs) or banned (PCBs and PCNs).

Polychloro-*n*-alkanes (PCAs) or chlorinated paraffins (CPs) constitute a class of industrial chemicals that have been produced since the 1930s for use as high-temperature lubricants in metalworking machinery and as flame-retardant plasticizers in vinyl plastics. Less common applications include the use as FRs in rubber, paints, and adhesives, and as sealants.

Data on CPs have been compiled, with particular emphasis on their physicochemical properties, environmental activity, and toxicology, in several review articles by Tomy *et al.* [170] and by Muir *et al.* [171].

The products comprise industrially prepared mixtures of the general formula C_xH(2x–y₂⁺)Cl_y, having carbon-chain lengths in the C₁₀–C₃₀ range and chlorine content from 30% to 70% by mass. They are divided into three categories: short-chain chlorinated paraffins¹³ comprising C₁₀–C₁₃ and with the limiting molecular formulas set at C₁₀H₁₉Cl₃ and C₁₃H₁₆Cl₁₂; medium-chain chlorinated paraffins¹⁴ comprising C₁₄–C₁₇ atoms; and long-chain CPs¹⁵ with more than C₁₈ or more carbon atoms. The three groups (sPCA, mPCA, and IPCA) are further sub-categorized by their weight content of chlorine (40–50%, 50–60%, and 60–70%) [172]. The many possible positions for the chlorine atoms and presence of chiral carbon atoms lead to a large number of potential positional isomers, enantiomers, and diastereoisomers. The level of chlorination of CPs varies between 30% and 72% by weight [173].

9.6.1 Use and Consumption of PCAs

Due to their varying carbon-chain lengths and chlorine percentages, PCAs provide a range of properties for different applications. The most common use for polychlorinated alkanes is as an extreme-pressure, anti-wear additive in lubricants used for metal machinery (particularly cutting oils). Polychlorinated alkanes are also frequently used as plasticizers in plastics (including vinyls, resins, and foams) and paints (including enamels, polyurethanes, and vinyl), and to a lesser degree in adhesives, caulks, and sealants. Polychlorinated alkanes are also used as FRs in rubber and plastic. A miscellaneous use for polychlorinated alkanes is as a water repellent.

The main uses for sPCAs in Europe are as extreme-pressure additives in metalworking fluid (~70%), FRs in rubbers (~9%), and plasticizers and FRs in paints and coatings (~5%). The main uses of mPCAs are as secondary plasticizers in PVC (~80%), as extreme-pressure additives in metalworking fluids (~9%), as additives to adhesive and sealants (5%) and as flame-retardant plasticizers in rubbers and other polymeric materials (~3%). Briefly, sCCPs are used mainly as extreme-pressure additives in metalworking fluids [174], mCCPs as secondary PVC plasticizers, and LCCPs as FRs for rubber and textiles.

The non-flammability of CPs, particularly at high chlorine contents, relies on their ability to release hydrochloric acid at elevated temperatures, thereby inhibiting the radical reactions in flames. CPs start to decompose at temperatures above 300°C and compounds with a higher degree of chlorination are more effective FRs.

Industrially, PCAs are synthesized by direct free-radical chlorination of different *n*-alkane fractions derived from petroleum distillation with molecular chlorine at elevated temperatures and pressures, and sometimes in the presence of UV-light.

¹³ Noted as SCCPs or sPCAs in the literature.

¹⁴ Noted as MCCPs or mPCAs in the literature.

¹⁵ Noted as LCCPs in the literature.

Hydrocarbon feedstocks include paraffins and other alkanes, olefins and other alkenes, and alkynes. The feedstocks most commonly used are normal paraffins and to a lesser degree, normal olefins. Paraffins are usually mixtures of components that vary in carbon-chain length. The normal paraffin fractions that are most commonly used in the manufacture of polychlorinated alkanes are short-chain, intermediate-chain, and long-chain fractions.

These reactions, which have low regioselectivity, yield complex formulations comprising mixtures of optical isomers and congeners [170]. As an example, Coelhan *et al.* [175] synthesized C_{10} PCAs with different degrees of chlorination for the first time and used them as individual standards for quantification analysis [176].

Since their introduction in the 1930s, the world production of PCAs has increased significantly. Historically, in 1964, the estimated annual world production was 38,000–50,000 tons; in 1977, 230,000 tons; and in 1985, 300,000 t;¹⁶ and, it increased by up to $1\% \text{ yr}^{-1}$ between 1989 and 1998 [177]. In the late 1990s, world annual production of sPCAs represented about 50,000 t [178].

However, the use of sPCAs in Europe decreased by 70% between 1994 and 1997, largely as a result of the countries signing up the OSPAR Convention decision to phase out the use of sPCAs. As a result of regulations on SCCPs, MCCP use has increased and eventually reached higher levels than SCCPs [179].

In 1998, North American production of sPCAs, mPCAs, and IPCAs reached 7900, 17,800 and 12,700 t, respectively [180, 181]. More data on the production, import, export, and use of CPs by some specific countries are available elsewhere [171].

In 2002, the EU Directive 2002/45/EC [182] restricted the use of sPCAs in metal- and leather-associated applications, and less than $15,000 \text{ t yr}^{-1}$ of sPCAs were manufactured in the EU. By contrast, global use of mPCAs has risen. In Europe, for example, the use of mPCAs already surpasses that of sPCAs [183].

9.6.2 Properties of PCAs

PCAs have physicochemical properties similar to those of other chlorinated POPs. Polychlorinated alkanes in general have high boiling points, low vapor pressures, low water-solubility values, and high chemical and thermal stability. The physical and chemical properties of PCAs appear to be strongly dependent on two factors: the carbon chain length and the degree of chlorination [176, 184, 185]. The m.p. of PCAs increases with the carbon-chain length and chlorine content. Consequently, at r.t., PCAs range from viscous colorless or yellowish dense oils with about 40% chlorine content to some LCCPs (C_{20} to C_{30} with a chlorine content of $>70\%$), which are white solids [176].

PCAs have very low vapor pressure and water solubility. The Cl substitution pattern affects the physicochemical properties of PCAs. In particular, water solubility increases with the degree of chlorination up to 5.

Generally, PCAs are hydrophobic and non-volatile, and are likely to be associated with particles in aquatic systems. PCAs are lipophilic in nature with $\log K_{ow}$

¹⁶ World Health Organization, WHO Environmental Health Criteria 181, WHO International Programme on Chemical Safety, Geneva, Switzerland, 1996.

values generally greater than 5. Vapor pressure and Henry's Law constant seem to decrease with the degree of chlorination and increasing carbon-chain length [185].

9.6.3 PCAs in the Environment

Data on PCA levels in the environment are generally limited compared to other organochlorine pollutants (e.g., PCBs) due to difficulties in quantifying complex mixtures of PCAs [186]. The wide range of PCA use and the improper disposal of products containing PCAs are likely to be the reasons for their ubiquitous presence in the environment. The release of PCAs into the environment could occur during production, storage, transportation, industrial use, and carry-off from manufactured products. Release could also occur from plastics, paints, and sealants in which they are incorporated by leaching, runoff, or volatilization from landfill, sewage-sludge-amended soils, or other waste-disposal sites. Of these, however, the major releases are thought to be from production use. These releases are collected in sewer systems and ultimately end up in the effluents of STPs.

PCAs are therefore ubiquitous in our daily environment and have been detected, for example, in the sealant products of doors and windows in office buildings [187] and in paints used for swimming pools and garages [188]. It is estimated that more than 200 commercial PCA formulations have been made available on the market [189].

Other releases could include use of gear-oil packaging; fluids used in hard-rock mining and equipment use in other types of mining; fluids and equipment used in oil and gas exploration; manufacture of seamless pipe; and metal-working and operation of turbines on ships.

As recognized persistent organic pollutants (POPs), PCAs are frequently detected in a wide variety of environmental matrices such as sediments [173, 190], soils, seawater [191], freshwater [181], aquatic biota [181], terrestrial biota [192], marine mammals [193] and human tissues [194], and in air [195, 196] in both industrial and non-industrial areas [173, 192, 197–204], although sCCPs are not found in air because of their low vapor pressures [196]. On a global scale, developed countries can be considered as the major source of PCAs. Very little is known about the regional levels of these contaminants, especially in regions outside North America, Europe, and Japan.

Analytical methodologies tested and applied for the determination of chlorinated paraffins have been reviewed [186, 205–207]. In general, the determination of PCAs is difficult because of the complexity of the mixtures and the enormous number of congeners in this class of pollutants as well as the numerous substances that could interfere with them [208]. The difficulties in analyzing PCAs have discouraged many environmental laboratories from studying this class of pollutants, and therefore only a few laboratories worldwide analyze PCAs. PCAs are analyzed by GC using an ECD detector, or by the more sophisticated high-resolution gas chromatography/electron capture negative ion-mass spectrometry (HRGC/ECNI-MS) [192]. HRGC/ECNI-MS was employed to measure concentrations of short and medium chain length polychlorinated *n*-alkanes

extracted from samples of water, river sediment, benthos, fish, soil, digested sewage, and earthworms.

The analysis of samples from 20 aquatic and eight agricultural sites indicated that short- and medium-chain-length polychlorinated alkanes were present in the following concentration ranges: sediment $<0.2\text{--}65.1\text{ mg kg}^{-1}\text{ dw}$, water $<0.1\text{--}1.7\text{ }\mu\text{g L}^{-1}$, fish $<0.1\text{--}5.2\text{ mg kg}^{-1}\text{ ww}$, benthos $<0.05\text{--}0.8\text{ mg kg}^{-1}\text{ ww}$, digested sewage $1.8\text{--}93.1\text{ mg kg}^{-1}\text{ dw}$, soil $<0.1\text{ mg kg}^{-1}\text{ dw}$, and earthworms $<0.1\text{--}1.7\text{ mg kg}^{-1}\text{ ww}$ [192]. PCAs were also determined in sample extracts using GC–NICIMS on a Thermo-Quest GCQ benchtop ion-trap instrument with methane as the reagent gas [192]. This could be employed to provide qualitative information on the nature of the principal PCA component in the mixture [192].

It is clear from some studies that these compounds are widely distributed in the UK environment, although it is not yet possible to fully assess the risks posed to either wildlife or the human population by their continued use [192].

9.6.4 Toxicology and Regulations of PCAs

CPs have attracted increasing attention in the last decade as they represent a potential “new” category of POPs [189, 209]. The limited biodegradation data suggest that PCAs are less persistent in water, sediments, or biota than other organochlorines. Greater bioconcentration factors were found for sPCAs, probably due to their greater water solubility. Moreover, highly chlorinated sPCAs are predicted to have the greatest BCFs because they are more hydrophobic and resistant to biotransformation than lower chlorinated PCAs and their accumulation is not hindered by large molecular size or extremely high K_{ow} , as observed for mPCAs and IPCAs [210].

sPCAs exhibit the highest toxicity among all PCA products and studies conducted on rats have classified them as being very toxic to aquatic organisms and carcinogenic [170]. Other studies detail data for CPs on lipophilicity/bioaccumulation [181, 211, 212], persistence [213], long-range transport [173], and toxicity [170].

There are currently no restrictions on the manufacture, processing, and use of CPs in the United States. In the United States, $C_{10}\text{--}C_{13}$ PCAs have been placed on the USEPA Toxic Release Inventory, in Canada they are classified as “Track 1” Priority Toxic substances under the Canadian Environmental Protection Act, and in Europe the $C_{10}\text{--}C_{13}$ PCAs are included in the list of priority substances in the field of water policy submitted by the Commission of European Communities for the European Parliament and Council Decision. In 2001, the EU listed short-chain CPs (SCCPs) as priority hazardous substances [214], and compelled member states to establish monitoring programs for surface water and ground-water [215].

Under the Toxic Release Inventory (40 CFR 372) in the United States and the National Pollutant Release Inventory (NPRI) in Canada, industries manufacturing or using some CPs are requested to register with the authorities. CPs are not regulated hazardous wastes under the Federal Resource Conservation and Recovery Act (RCRA) system, although waste oils containing SCCPs are considered as hazardous wastes in some states.

However, the WHO stated in 1996, with reference to CPs, that “reported results should be regarded only as estimates of the true values” since environmental analysis has been hindered by numerous technical challenges. The complexity of CP analysis may explain why these compounds are not a common choice of analytical study. There is therefore a growing need to establish quality-assured analytical methods for determining CPs in environmental samples [206].

9.7 Organophosphate Flame Retardants (OPFRs)

Organophosphate flame retardants (OPFRs) have been used for several decades in many industries, including in the production of dyes, varnishes, adhesives, synthetic resins, polyvinyl chloride, hydraulic fluids, plastics, and textiles. Their importance in recent times has grown due to the significantly reduced use of polybrominated diphenyl ethers (PBDEs) [216].

OPFRs are medium to highly polar molecules, and consequently, they tend to partition into the water phase [155, 217–219]. Chlorinated OPFRs, such as tris(2-chloroethyl) phosphate (TCEP), tris(2-chloro-1-methylethyl) phosphate (TCPP), and tris(1,3-dichloro-2-propyl) phosphate (TDCP), are preferentially used as flame-retarding additives in polyurethane foam (see Figure 9.9). Non-halogenated OPFRs, for example, tris(2-butoxyethyl) phosphate (TBEP), tri-*iso*-butyl phosphate (TiBP), and tri-*n*-butyl phosphate (TnBP), are used as plasticizing, antifoaming, or flame-retarding agents in plastic materials and hydraulic fluids used in many household products (e.g., plastics, textiles, furniture, electronics, and construction materials) [219].

OPFRs, such as TPP and TDCP, are now among the most commonly used PBDE alternatives in consumer products containing polyurethane foam [120–122, 220].

In 2012, Van der Veen and de Boer [121] published a review on OPFRs, providing an overview of their properties, production, environmental occurrence, toxicity, and analytical methods used for determining these. Of the OPFRs, only the chlorinated ones have proved to be carcinogenic.

9.7.1 Use and Demand of OPFRs

The Organophosphate esters tris-(2-chloroethyl)-phosphate (TCEP) and tris-(2-chloropropyl)-phosphate (TCPP) are widely used as FRs and fire-preventing agents, for example, in polyurethane foam. Most of the TCPP and TDCpP produced in the EU in 2000 were indeed used in the production of flexible and/or rigid PUR foam in the automotive industry, construction, and furniture.

An alkyl phosphate ester, tris(2-chloroethyl)phosphate (TCEP), is used as a flame-retardant plasticizer and viscosity regulator in polyurethanes, polyester resins, polyacrylate textile back-coating formulations, PVC and cellulose ester compounds, and coatings. The main industrial branches in which TCEP has been used are building (e.g., roofing insulation, accounting for more than 80% use in the EU), furniture, and textiles. In addition, uses are reported in the manufacture

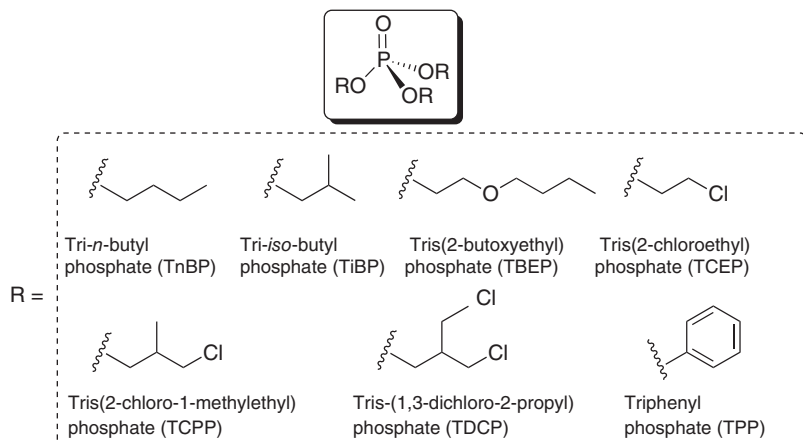


Figure 9.9 Structure of the most common organophosphate flame retardants (OPFRs).

of cars, railways, and aircrafts, as well as in professional paints, varnishes, and lacquers. The production volume, worldwide, of TCEP was about 9000 t in 1989 and declined to less than 4000 t in 1997.¹⁷

All commercial TCPP is produced by the reaction of phosphorus oxychloride with propylene oxide (epichlorohydrin) followed by purification. TCPP consists of four isomers, with a variable relative ratio in the commercial products, although their physical-chemical properties and toxicological characteristics are similar. TCPP production and use has continued to grow since the mid-1960s when it was first commercialized. Its growth has been a reflection of polyurethane tonnage growth and the fact that TCPP has replaced other FRs, for example, tris(chloroethyl) phosphate (TCEP). For TCPP, the production volume was about 40,000 t in 1997 and 36,000 t in 2000 [221].

Tris-(1,3-dichloro-2-propyl)-phosphate (TDCPP) is used as a FR in a range of plastic foams, resins, and latexes. TDCPP is manufactured from epichlorohydrin and phosphorus oxychloride. The commercial TDCPP contains trace amounts of tris-(2,3-dichloropropyl)-phosphate. Global tris(1,3-dichloroisopropyl)phosphate (TDCPP) demand has been estimated at 8000 t yr⁻¹ and continues to grow.

9.7.2 Properties of OPFRs

TCEP is a non-volatile liquid at room temperature (vapor pressure = 114×10^{-5} Pa at 20 °C); under normal conditions, inhalation exposure is related mainly to dusts containing TCEP formed primarily by abrasion.

Tris(1-chloro-2-propyl) phosphate (TCPP) is a colorless liquid used mainly in polyurethane foams. It is not volatile. Its solubility in water is 1.6 g L⁻¹, it is soluble in most organic solvents, and it has a log K_{ow} partition coefficient of 2.59.

¹⁷ WHO 1998 Flame Retardants: Tris(Chloropropyl) Phosphate And Tris(2- Chloroethyl) Phosphate http://www.who.int/ipcs/publications/ehc/who_ehc_209.pdf.

TDCPP is a viscous colorless liquid used as a FR in a range of plastic foams, resins, and latexes. Not volatile, its solubility in water is 0.1 g L^{-1} , it is soluble in most organic solvents, and it has a $\log K_{ow}$ partition coefficient of 3.8.

TCPP is analyzed by GC/MS. Concentration of TCPP from water prior to analysis can be achieved using Amberlite XAD resin, followed by extraction with various organic solvents.

OPFRs, used as replacements for PBDE mixtures that are being phased out, are ubiquitous in the environment. They have been detected at high concentrations in residential dust, suggesting that widespread human exposure may be associated with altered hormone levels and decreased semen quality in men [222, 223].

9.7.3 OPFRs in the Environment

Chlorinated and non-halogenated OPFRs have been found to be occasionally present in US groundwater intended for drinking water [20, 218]. The most abundant OPFR was TnBP, with a maximum concentration of 740 ng L^{-1} . Conversely, chlorinated OPs were below 50 ng L^{-1} [20, 218]. The occurrence of OPFRs has also been investigated in aquifers impacted by landfill leachates, and in managed aquifer recharge (MAR) sites [155, 219, 224–226]. These compounds are frequently found in landfill leachate-affected groundwater. Fairly high median concentrations of TCEP (141 ng L^{-1}) and TCPP (191 ng L^{-1}) [219], and up to $3.8 \text{ } \mu\text{g L}^{-1}$ of TnBP were measured [65] in groundwater below landfill sites. River-bank filtrates contained up to $1.8 \text{ } \mu\text{g L}^{-1}$ of TCPP and TBEP. However, concentrations of nonhalogenated OPs have been observed to have an inverse relationship with river proximity, which could be attributed to biotransformation and/or sorption processes [219].

TCEP has been identified in indoor and outdoor air, dust, drinking water, and surface water and groundwater as well as in various food products. It has also been detected in polyurethane foam found in furniture and in toys. TCEP as a typical micropollutant, is currently present in surface water, WWTPs, oceans, and drinking water from ng L^{-1} to $\text{ } \mu\text{g L}^{-1}$ [227–230] due to a low elimination rate [229, 231–233].

The presence of TCEP has been attributed primarily to emissions from indoor sources [234]. Studies on distribution in dust in a variety of indoor environments were performed by Marklund *et al.* [235] and Hartmann *et al.* [236]. Several instances of high amounts of organophosphates including TCPP and TCEP were detected selectively in different environments [221].

TCEP has been measured in dust and particulate matter in indoor locations in Sweden and Germany within the range ≤ 10 to 2200 mg kg^{-1} . The median concentration has been estimated at 0.6 mg kg^{-1} [234, 235]. TCEP was also measured in indoor air in homes, offices, schools, and cars at values ranging from not detected to as high as 6000 ng m^{-3} , with the highest value found in a school in Germany. The median concentration was 10 ng m^{-3} . In a study on chemicals found in electrical and electronic products, TCEP was detected in emissions from television sets at <0.01 – $0.3 \text{ } \mu\text{g h}^{-1}$ per set.¹⁸

18 Malmgren-Hansen, B., Olesen, S., Pommer, K., Funch, L.W., Pedersen, E., Willum, O., Olsen, S. 2003 Emission and evaluation of chemical substances from selected electrical and electronic

Although physically present within the polymer matrix, TCEP can be emitted due to its migration to the surface and release from plastic products, giving rise to an additional potential source of exposure. This phenomenon is called “bloom-ing,” which refers to the diffusion of an ingredient in rubber or plastic material to the outer surface after curing. Tris phosphates in general are known to bloom from rigid plastics.

Dermal exposure can occur from direct contact with, for example, furniture coverings as well as with dust. The only available data is from the National Research Council [237], which has estimated dermal exposures of 0.003 and 1.5 mg kg⁻¹ bw d⁻¹ for substances similar to TCEP, tris(1,3-dichloropropyl-2)phosphate (TDCP) and tris-monochloro-propyl phosphate (TCPP), respectively.

Oral exposure can occur due to dust intake, hand-to-mouth transmission, and contamination of articles for daily use, for example, toys that can be put into the mouth. Relevant for the oral route, TCEP was also found in drinking water, where concentrations ranged from not detectable to 52 ng L⁻¹.¹⁹

Traces of TCPP have been detected in industrial and domestic effluents but not in surface waters. Traces of TDCPP have been detected in sewage effluents, river water, seawater, drinking-water, and sediment as well as in fish. TDCPP has been found in some samples of human adipose tissue. Traces of TCPP have been also detected in raw peaches, raw pears, and fish.

TCPP was found at concentrations between 1 and 132 ng L⁻¹ in groundwater affected by well injection of tertiary-treated wastewater in Spain [155, 224]. Conversely, higher concentrations of TCPP (up to 1000 ng L⁻¹) were measured in a MAR site in Arizona [226]. In a similar way to PFASs, landfill leachates may contribute, at least locally, to groundwater contamination by FRs, as these compounds were determined at considerably high levels in water impacted by landfill leachate [64, 65, 219, 238–240].

9.7.4 Toxicology and Regulations of OPFRs

Recently, Schang *et al.* [241] showed that organophosphate FRs act as endocrine-disrupting chemicals in an *in vitro* study.

Basal progesterone production was significantly increased (10 μM, 1.5 to 3-fold) by 2-ethylhexyl diphenyl phosphate, isodecyl diphenyl phosphate, isopropylated triphenyl phosphate, *tert*-butylphenyl diphenyl phosphate, and tricresyl phosphate, while BDE-47, triphenyl phosphate, and tri-*o*-cresyl phosphate had no effect.

Exposure to TCEP and TCPP may arise from occupational contacts and environmental sources (drinking water, surface water, indoor air, and food). The two FRs tested, TCEP and TCPP, are of interest for regulation and risk assessment.

products. Survey of Chemical Substances in Consumer Products, No. 32. Copenhagen (DK): Danish Ministry of Environment. <http://eng.mst.dk/media/mst/69115/32.pdf>.

19 Canadian Report on TCEP, 2009. Ethanol, 2-chloro-, phosphate (3:1)(Tris(2-chloroethyl) phosphate (TCEP) <http://www.chemicalsubstanceschimiques.gc.ca/challenge-defi/summarysommaire/batch-lot-5/115-96-8-eng.php>.

For TCEP, which has been used for a longer time period, the existing data are more complete, as compared to TCPP [242]. TCEP is a non-volatile liquid at room temperature, and thus, under normal conditions, inhalation exposure is related mainly to dusts containing TCEP formed primarily by abrasion.

The majority of toxicological studies of TCEP have dealt with carcinogenic [243], neurotoxic [244, 245], mutagenic [246–248], and tumoral properties, with high mg L⁻¹ [243] *in vivo* except Föllmann and Wober [221], who previously studied cytotoxic, genotoxic, mutagenic, and estrogenic effects of TCEP *in vitro* with various concentrations from low ng L⁻¹ to high mg L⁻¹. These researches failed to detect any effect at ng L⁻¹ and µg L⁻¹ concentrations.

Results demonstrated that TCEP at environmental concentration affected cell-cycle regulatory protein expression in primary cultured rabbit renal PTCs [249]. Studies in animals showed the carcinogenic potential of TCEP [243, 250]. Because of human health concerns, the use and the production of TCEP have been significantly reduced during the last decade [221]. TCEP has been replaced with TCPP and TDCP, mostly in the manufacture of polyurethane foam.

Based on experimental data for exposure to “neat” TCPP or due to handling of foam containing TCPP, oral absorption has been reported at around 80%, whereas the dermal-absorption values were found to be 23%. For the inhalation route, 100% absorption is assumed. TCPP is of low acute toxicity via the inhalation and dermal route. No data are available on the kinetics and metabolism of TCPP in mammals. No studies of the effects of TCPP on humans are available. A skin-sensitization study showed that TCPP has no sensitizing properties. The reproductive toxicity, immunotoxicity, and carcinogenic potential of TCPP have not been investigated. The results of *in vitro* and *in vivo* mutagenicity studies investigating an appropriate range of end-points indicate that TCPP is not genotoxic.

TDCPP exposure gave some indications of immunotoxicity in mice but only at high doses. Kinetic studies in rats using ¹⁴C-labeled TDCPP showed the radio label to be distributed throughout the body following oral or dermal administration. The major metabolite of TDCPP identified in the urine of rats was bis(1,3-dichloro-2-propyl) phosphate. Limited studies on occupational exposure of humans are available but they add little to the knowledge of the safety aspects of TDCPP.

TDCPP is of low to moderate acute toxicity by the oral route and of low acute toxicity by the dermal route. The sensitization potential of TDCPP has not been investigated. The potential of TDCPP to affect human male reproductive ability is unclear in view of testicular toxicity in rats and a lack of effect on male reproductive performance in rabbits. The possible effect on female reproduction has not been investigated. No teratogenicity was seen. Overall, the mutagenicity data show that TDCPP is not genotoxic *in vivo*. TDCPP exposure offered some evidence of immunotoxicity in mice but only at high doses. Limited human studies following occupational exposure are available but are inconclusive concerning the safety aspects of TDCPP.

9.8 Corrosion Inhibitors: Benzothiazoles and Benzotriazoles

Both benzotriazoles and benzothiazoles are high volume production chemicals. They were recently measured in human urine from a multicountry study in the United States, Greece, Vietnam, Korea, Japan, China, and India [251].

Because of the water solubility of benzotriazoles and benzothiazoles, LC/MS and LC-MS/MS methods have been recently developed for their measurement in environmental waters. Corrosion inhibitors were present at considerably lower concentrations, in the ng L^{-1} range, in riverbank filtrates [252, 253] and in an aquifer recharged with reclaimed water [254].

9.8.1 Benzotriazoles

Benzotriazole (BT) and its derivatives are complexing agents that are widely used as corrosion inhibitors (e.g., in engine coolants, aircraft deicers, or antifreeze liquids) and for silver protection in dishwashing detergents (see Figure 9.10). Their use as anticorrosive agents in aircraft deicing and anti-icing fluids during winter also constitutes an important source of these compounds reaching the environment [255].

The two common forms, 1*H*-benzotriazole (BT) and tolyltriazole,²⁰ are soluble in water, resistant to biodegradation, and only partially removed in wastewater treatment. Studies indicate that they are ubiquitous environmental contaminants. Benzotriazole and tolyltriazole ranged from 840 to 3605 ng L^{-1} and 2685 to 5700 ng L^{-1} , respectively, in sewage effluents and from 0.6 to 79.4 ng L^{-1} and <0.5 to 69.8 ng L^{-1} , respectively, in drinking water [256]. Wolschke *et al.* [257] reported the first findings of benzotriazoles in the marine environment.

Concentrations of benzotriazoles in groundwaters were reviewed by Postigo and Barceló [5]. The highest concentrations, occasionally reaching the mg L^{-1}

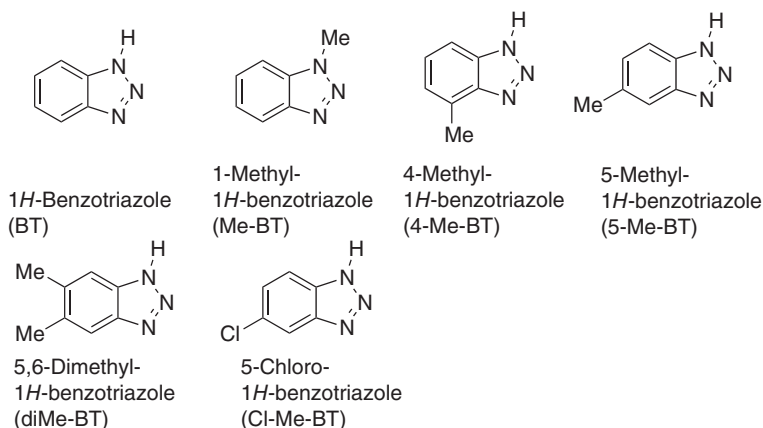


Figure 9.10 Chemical structure of benzotriazole (BT) and derivatives.

²⁰ A mixture of 4- and 5-methyl-1*H*-benzotriazole.

range, were found in groundwater below or close to sites of aircraft deicing and the application of anti-icing fluids [258, 259]. In karst aquifers, BT and tolyltriazole were not ubiquitous, but their concentrations reached up to 3242 and 213 ng L⁻¹, respectively [260, 261]. Benzotriazol and tolyltriazole were also measured in groundwaters used for drinking water in Europe. These corrosion inhibitors were present in half of the groundwater samples analyzed. The concentrations of these compounds were occasionally above 0.1 µg L⁻¹, and they were detected at maximum concentrations of 1032 and 516 ng L⁻¹, respectively [18]. In a US nationwide study, 5-methyl-1*H*-benzotriazole (5-Me-BT) was rarely present in groundwater used as a drinking-water supply source, and concentrations found were always below the method reporting limit [218].

New evidence has emerged for estrogenic effects *in vitro* but, so far, not *in vivo*, in recent fish studies. In addition, some evidence indicates that benzotriazole may be a human carcinogen, and Australia now has a drinking-water guideline limit of 7 ng L⁻¹ for tolyltriazole [262].

9.8.2 Benzothiazoles

Benzothiazoles are a class of chemicals produced in large volumes that are used as anticorrosives and in the manufacture of rubber and other products (see Figure 9.11). Benzothiazoles can be found in rubber materials, herbicides, slimicides, algacides, fungicides, photosensitizers, azo dyes, drugs, deicing/anti-icing fluids, and food flavors [263].

Benzothiazoles have wide applications as fungicides, herbicides, accelerators for vulcanization of rubber, biocorrosion inhibitors, dye production, and lumber and leather production; their derivatives occur as 2-substituted benzothiazoles (2-mercapto-, 2-hydroxy-, 2-sulfonic acid-, 2-methyl-) [264, 265].

Benzothiazoles are another group of CECs that frequently occur in urban water cycles [265, 266]. These are often detected in river waters and most importantly their occurrence could also be indicative of street runoff because of their use in rubber and tire manufacturing industries where they are employed as vulcanization accelerators [267, 268].

These compounds are also widely employed in the leather and paper industries as fungicides, where they are used instead of chlorophenols [267].

In particular, STP effluents appear to be one of the major release routes of these compounds into natural waters [265]. BT and MTBT have been detected in various environmental compartments [267] as a result of the degradation of parent compounds in industrial processes [265]. However, little is known about their fate and effects. A systematic study on the occurrence of benzothiazoles in municipal wastewater [266] has shown that this is an important class of trace

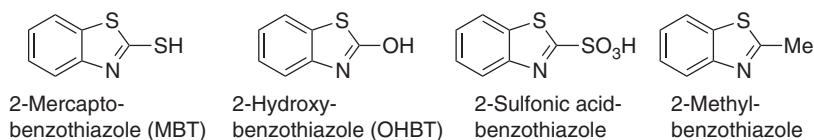


Figure 9.11 Chemical structure of benzothiazole and derivatives.

contaminants in this kind of wastewater. Thus, Reemtsma *et al.* [267] concluded that the 2-substituted benzothiazoles employed in industrial processes are not completely removed by biological wastewater treatment, which poses problems for the aquatic environment due to their limited biodegradability and potential toxicity [267].

Their limited biodegradability and potential aquatic toxicity suggest that they are of higher environmental concern than previously recognized [267]. BT and OHBT are generally considered to be biodegradable, whereas 2-MTBT is recalcitrant [267].

9.9 Polycyclic Aromatic Hydrocarbons (PAHs)

PAHs are not produced for commercial purposes. They are naturally formed during volcanic eruptions and forest fires. However, most PAHs originate from anthropogenic sources, such as the incomplete combustion of fossil fuels, wood and waste; automobile exhaust; and petroleum derivative spills [269].

PAHs consist of two or more fused aromatic rings made up of carbon and hydrogen atoms (see Figure 9.12). The ring systems can be present in multiple configurations and may be either substituted or unsubstituted. PAHs range from semi-volatile molecules to molecules with high boiling points.

Thus, they may be found both in the gas and the particulate phase of ambient air or in mixtures of both phases. About 500 different PAHs have been detected in air, but often the measurements focus on benzo[*a*]pyrene (B[*a*]P) as a representative of the whole PAH family [270].

Diffuse contamination of PAHs occurs via adsorption to airborne solid particles [271]. Wind transports the particles to distant locations where they are deposited directly onto the soil or indirectly to soil through vegetation. Due to their low solubility, PAHs tend to be deposited into sediments and soil. The binding affinity of PAHs to soil organic matter is determined by the $\log K_{ow}$ values. PAHs with high molecular mass tend to have a higher affinity for soil organic matter. Overall, low-molecular-weight PAHs (two-ring, three-ring, and four-ring PAHs) have been the prevailing species found in groundwater.

Naphthalene, the simplest PAH, was the most ubiquitous and abundant VOC (maximum concentrations of $334 \mu\text{g L}^{-1}$) in groundwater samples collected from alluvial plains in China [272]. Naphthalene, was the most abundant compound followed by phenanthrene, in groundwater affected by a wetland that was used for sewage treatment in China [273]. The reported average concentrations were 0.3 and $0.12 \mu\text{g L}^{-1}$ in the case of naphthalene and phenanthrene, respectively.

Three-ring and four-ring PAHs, that is, anthracene, chrysene, phenanthrene, and fluoranthene were the main species that contributed to total PAH concentrations ($0.2\text{--}1.6 \mu\text{g L}^{-1}$) in groundwater impacted by a petrochemical industry in Pakistan [274]. In a recent study conducted in a city in China, the main contributing species to the total PAH concentrations ($2.14\text{--}22.3 \mu\text{g L}^{-1}$) in groundwater were the four-ring species fluoranthene, pyrene, and benzo[*a*]anthracene, and the five-ring benzo[*k*]fluoranthene [275].

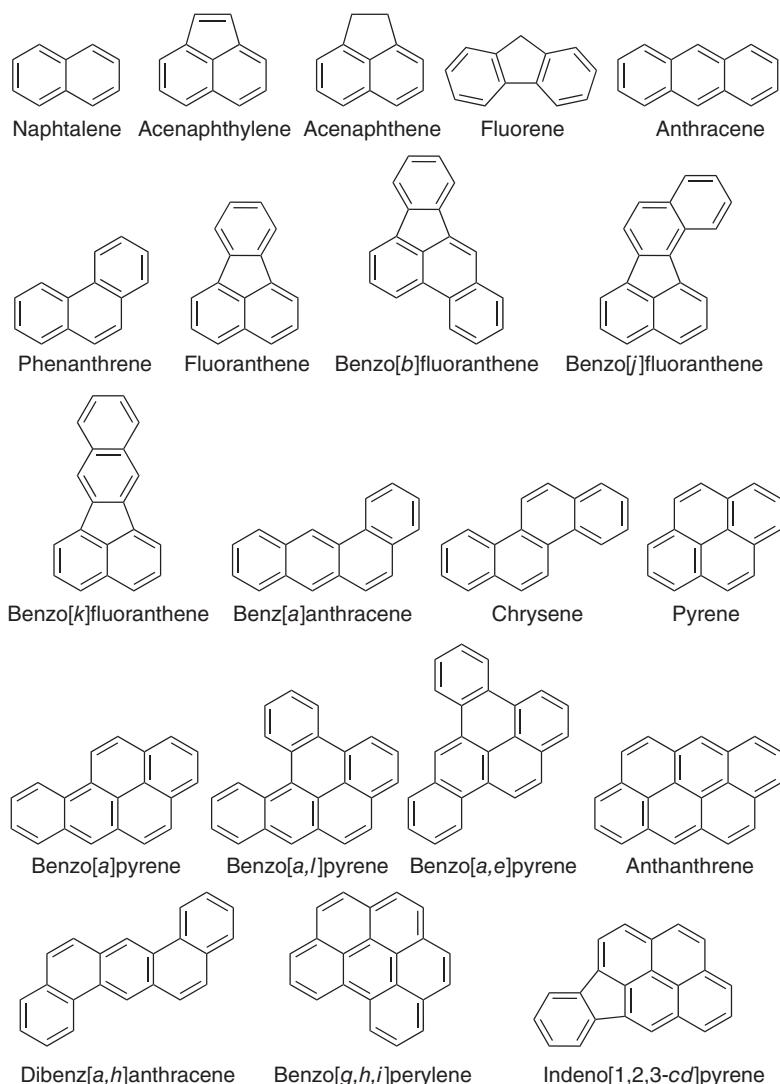


Figure 9.12 The 16 priority pollutant PAHs listed by USEPA.

Trace levels of PAHs (in the low ng L^{-1} range) have occasionally been detected in an aquifer recharged by tertiary treated wastewater [155, 224]. The dominant PAHs in groundwater in China were reported to be phenanthrene, fluorene, and fluoranthene that originated from both petrogenic and pyrolytic sources [276].

It is estimated that soil receives $0.7\text{--}1 \text{ mg m}^{-2}$ of PAHs by atmospheric emissions [277, 278]. In 2009, Zhang and Tao [279] estimated the total global atmospheric emission of the 16 PAHs listed by the USEPA to be $520,000 \text{ t yr}^{-1}$.

Once in the environment, PAHs can be oxidized by chemicals and/or microbiological processes to form nitrated PAHs (nitro-PAHs) and oxygenated PAHs

(oxy-PAHs). These compounds, together with alkylated-PAH, can also be directly emitted from combustion sources.

Substituted PAHs are present at measurable concentrations in wastewater-plant effluents, river waters, and soils [275, 280]. Nitro- and oxy-PAH are more water soluble and less lipophilic than non-substituted PAHs, and therefore, they may be more mobile in the subsurface than are parent compounds. However, according to their physicochemical properties, PAH derivatives are still expected to partition into solid environmental matrices [281]. A leaching risk exists for compounds that accumulate in soil as a result of PAH degradation [282]. Nitro-PAH occurrence in groundwater in China was recently investigated, and in all cases, the compounds investigated were below the detection limit [275]. Oxy-PAHs were detected in groundwater impacted by a gas plant. The most abundant and ubiquitous oxy-PAH found in this study was acenaphthenequinone (maximum concentration of $1.9 \mu\text{g L}^{-1}$) [283].

They are potential carcinogens and/or mutagens, and therefore, their levels in water are subject to regulation (see Table 9.9).

9.10 Volatile Organic Compounds (VOCs)

The presence of VOCs in the aquatic environment has been investigated since the 1970s. Since then, a nationwide groundwater survey have been carried out in the United States to evaluate VOC occurrence [290, 291]. The main groups of VOCs usually found in groundwater are trihalomethanes (THMs), solvents, and gasoline components. Leaching of VOCs into groundwater is directly related to aquifer properties and land use, which also determines VOC sources. Owing to the environmental levels and their toxicity, and in some cases, their bioaccumulation potential, VOCs constitute the main group of synthetic organic contaminants included in water regulations in Europe and in the United States (see Table 9.9).

Chloroform (CHCl_3) is a common groundwater pollutant in both urban and rural areas that has a natural and an anthropogenic origin [292]. Concentrations of trichloromethane of between 0.2 and $4.3 \mu\text{g L}^{-1}$ were found in groundwater beneath coniferous forests in Denmark, where local groundwater quality criteria for this compound is set to $1 \mu\text{g L}^{-1}$ [293]. In a US nationwide study, chloroform was the most ubiquitous and abundant VOC [291]. This observation is in agreement with the findings reported by Barlow *et al.* [294] in shallow groundwater in the Memphis urban area. Chloroform concentrations above $0.02 \mu\text{g L}^{-1}$ were measured in 36.5% and 17.6% of US public and domestic well samples, respectively [289]. Quantified chloroform concentrations in this study were usually below $1 \mu\text{g L}^{-1}$ [289]. In a groundwater survey in China, chloroform was present in 17% of the investigated samples and reached maximum concentrations of $98.8 \mu\text{g L}^{-1}$ [272].

Bromine-containing trihalomethanes were less ubiquitous and abundant than chloroform in groundwater intended for drinking water in the United States. Among the brominated trihalomethanes, bromodichloromethane was the most widespread in the samples analyzed [289].

Table 9.9 Standard, guideline, and concentration values ($\mu\text{g L}^{-1}$) found in groundwater for industrial chemicals.

Industrial chemical	EPA ^{a)} MCL	Europe ^{b)} AA/MAC	WHO ^{c)} guideline	Conc.	[References]
Benzene	5	10/50	10	0.3–1900	[272, 284]
PBDEs	–	n.a/0.14	–	0.0002–0.23	[146, 285]
Carbon tetrachloride	5	12/n.a.	4	0.01–2377	[272, 284]
1,2-Dichlorobenzene	600	–	1000	0.04–0.14	[65, 272]
1,4-Dichlorobenzene	75	–	300	0.21	[272]
1,2-Dichloroethane	5	10/n.a.	30	0.01–147	[272, 284]
1,2-Dichloroethene	700/100	–	50	7.73/0.66	[272]
1,1-Dichloroethene	7	–	–	1.75	[272]
Dichloromethane	5	20/n.a.	20	0.004–316	[272, 284]
DEHP	6	1.3/n.a.	8	0.06–46	[65]
Naphthalene	–	2/130	–	0.3–334	[155, 272, 273, 275]
4-Nonylphenol (4-NP)	–	0.3/2.0	–	0.05–3850	[18, 286]
Octylphenol	–	0.1/n.a.	–	0.001–1.8	[18, 286]
Pentachlorobenzene	–	0.007/n.a.	–	0.0003–0.002	[155]
Pentachlorophenol	1	0.4/1	9	0.418–6000	[287, 288]
Benzo[a]pyrene	0.2	0.00017/ 0.27	–	0.0004–0.31	[65, 155]
PCBs	0.5	–	–	<0.1	[285]
Styrene	100	–	20	n.d.	[272]
Tetrachloroethene (PCE)	5	10/n.a.	40	0.01–6000	[272, 284, 286]
Toluene	1	–	700	0.003–5100	[272, 284]
Trichloroethene (TCE)	5	10/n.a.	20	0.002–230	[272, 284, 286]
Trichlorobenzenes	70	0.4/n.a.	–	0.0004–0.45	[272, 272]
1,1,1-Trichloroethane	200	–	–	0.87	[272]
1,1,2-Trichloroethane	5	–	–	0.03–40	[272, 284]
Chloroform	80	2.5/n.a.	300	0.02–130	[272, 289]
PFOS and its derivatives	–	0.00065/36	–	0.004–0.135	[18]
Hexabromocyclododecane	–	0.5-0.05	–	0.0003–0.0006	[285]
Xylenes	10	–	500	0.01–4000	[272, 284]

a) MCL = maximum contaminant level; Ref. [6].

b) AA/MAC = Annual average/maximum allowable concentration; Ref. [7]

c) Ref. [8].

TCE, 1,1,1-trichloroethane (TCA), 1,1-dichloroethane (1,1-DCA), PCE, and dichloromethane (DCM) are solvents usually present in groundwater. PCE, TCE, and TCA were the most abundant and frequent solvents detected in US aquifers [291]. On the contrary, 1,2-DCA, 1,2-dichloropropane, TCE and DCM with maximum concentrations of 147, 197, 107, and $36 \mu\text{g L}^{-1}$, respectively, were the

most ubiquitous solvents in the groundwater of eastern China [272]. TCE was widespread in UK groundwater, which registered concentrations in the $\mu\text{g L}^{-1}$ range in an aquifer impacted by a landfill leachate [65].

The gasoline oxygenate MTBE and the gasoline hydrocarbons toluene and benzene are the most commonly detected gasoline components in groundwater [272, 295]. According to a recent study, MTBE and benzene concentrations in groundwater intended for drinking water in the United States, which are usually below 20 and $1 \mu\text{g L}^{-1}$, respectively, do not pose a health risk [296]. Concentrations up to 74 and 6 mg L^{-1} for benzene and toluene, respectively, were measured in groundwater from an industrial contamination site [295].

Refrigerants, such as dichlorodifluoromethane (CFC-12) and trichlorofluoromethane (CFC-11), have been also detected at the $\mu\text{g L}^{-1}$ level in US groundwater [297, 298]. The worldwide occurrence and fate of chlorofluorocarbons in groundwater were reviewed by Höhener *et al.* [299].

9.10.1 Hazardous Compounds Originating from Oil Products

Crude oils are heterogeneous mixtures of hydrocarbons formed underground under high pressure from the remains of organic material. They can be refined into a multitude of products.

The main use of oil is as an energy source for vehicles, heating, and electricity production, as approximately 34% of the global energy demand is met by oil products. Crude oil is also used as a raw material in many man-made materials, such as plastics, paints, and solvents. Oil is produced globally in staggering quantities, as global oil demand which was 92.9 megabarrels per day in 2015, is foreseen to increase to 110 megabarrels in 2035. Crude oil is perhaps globally the most exploited non-renewable natural resource. Accordingly, substances derived from crude oil are the most common polluters of the environment.²¹

Crude oil is found only in a number of locations on earth, and its uneven distribution requires a vast transportation network. The most common type of petroleum contamination in the environment, however, is from sources of smaller volumes. Leaking heating oil containers, gasoline station tanks, and lines; improper handling of waste; and small accidental spills comprise most of the oil pollution in soil, waterways, and groundwater. Natural seeps are the largest contributors of oil in the sea, at 600,000 t of oil each year. Oil release to the sea by human activities is almost equivalent, at 480,000 t each year.²²

As for soil, the European Environment Agency estimated in 2006 that crude oil was the most important pollutant of the investigated contaminated sites, at 33.7%, which was second only to heavy-metal pollution.

The monoaromatic compounds benzene, toluene, ethylbenzene, and xylene, commonly found in crude oil, are often jointly called BTEX compounds. The most harmful of these compounds is benzene, which is a known carcinogen. Most of the highly volatile BTEX compounds released by human activity originate from

21 Organization of the Petroleum Exporting Countries (OPEC). 2011. World Oil Outlook. http://www.opec.org/opec_web/static_files_project/media/downloads/publications/WOO_2011.pdf.

22 Committee on Oil in the Sea, National Research Council (2003) Oil in the sea III: inputs, fates, and effects. <http://www.nap.edu/catalog/10388.html>.

fuel use and end up as pollutants in the air. Inhaling BTEX-polluted air is also the greatest hazard to humans. Oil products are often readily utilized by environmental microbes. Thus, biological treatment methods are typically effective at oil-polluted sites, and many promising, large-scale studies confirm that bioremediation is a feasible, cost-effective method for cleaning up oil contamination *in situ* [300].

9.10.2 Gasoline Additives: MTBE

Gasoline additives increase gasoline's octane rating or act as corrosion inhibitors or lubricants, thus allowing the use of higher compression ratios for greater efficiency and power. Types of additives include metal deactivators, corrosion inhibitors, oxygenates, and antioxidants. Fuel additives in the United States are regulated under section 211 of the Clean Air Act. EPA requires the registration of all fuel additives that are commercially distributed for use in highway motor vehicles in the United States. Some additives are harmful and are regulated or even banned in some countries.

The major use of MTBE is as a petrol additive, with production and consumption for this purpose having increased markedly in the 1990s in most parts of the developed world. MTBE is added to petrol at levels of up to 15% by volume as an oxygenate to improve combustion and to lower exhaust emissions, particularly carbon monoxide emissions.

The main physicochemical properties of MTBE are boiling point 55.2 °C, vapor pressure 33.5 kPa at 25 °C,²³ water solubility 48 g L⁻¹ at 25 °C,²⁴ log K_{ow} partition coefficient 1.24, and Henry's law constant 5.95×10^{-2} kPa m³ mol⁻¹.

From a drinking-water perspective, one of the most important aspects of MTBE is their objectionable taste and odor. The taste and odor readings reported in four recent studies were in the range of 24–135 and 15–180 µg L⁻¹, respectively.²⁵

Fugitive emissions from petrol refineries and petrol filling stations are major environmental point sources of MTBE, whereas vehicles themselves emitting sufficient MTBE is a significant source in dense traffic areas. Surface water can be contaminated by petrol spills and by the use of petrol-powered boats. Spills and leaking storage tanks can cause more serious problems in groundwater. MTBE is seen as a potentially serious long-term threat to drinking-water supplies as it is widely used at high concentrations in petrol.

MTBE is resistant to chemical and microbial decomposition in water. In surface water, MTBE is usually removed very rapidly due to its high volatility. In groundwater, it is more persistent than in surface water because its volatilization to air is reduced or eliminated. MTBE does not adsorb to soil particles to a great degree and is considered mobile.

23 Mackay, D., Shiu, W.Y., Ma, K.C. (1993) Illustrated handbook of physical-chemical properties and environmental fate of organic chemicals. Vol. 3. Volatile organic chemicals. Boca Raton, FL, Lewis Publishers. p. 916.

24 Budavari, S. et al. (1996) Methyl-*tert*-butyl ether, in The Merck index, 12th edn. Whitehouse Station, NJ, Merck & Co. p. 1611.

25 WHO2005 http://www.who.int/water_sanitation_health/dwq/chemicals/MTBE200605.pdf.

In Canadian drinking-water supplies, MTBE was detected in groundwater at 250 locations and in every Canadian province. Levels ranged from <0.005 to >3.4 mg L^{-1} , and 60% of samples contained MTBE at concentrations above 0.02 mg L^{-1} . The use of MTBE in petrol has been more widespread and of longer duration in the United States than in Canada. It has been estimated that 30% of the US population lives in areas where MTBE is regularly added to the petrol; however, in these areas, it is unlikely that the MTBE level in drinking water exceeds 2 $\mu\text{g L}^{-1}$ in 95% of cases, with possibly 5% showing higher levels in the vicinity of major spills and leaks [301].

9.11 Other Industrial Chemicals

9.11.1 Siloxanes

Siloxanes have become a relatively new area of research. They include cyclic siloxanes, octamethylcyclotetrasiloxane (D4), decamethylcyclopentasiloxane (D5), dodecamethylcyclohexasiloxane (D6), and tetradecamethylcycloheptasiloxane (D7), and linear siloxanes (see Figure 9.13). They are used in a number of products, such as cosmetics, deodorants, soaps, hair conditioners, hair dyes, car waxes, baby pacifiers, cookware, cleaners, furniture polishes, and water-repellent windshield coatings. For example, decamethylcyclopentasiloxane is an odorless, colorless liquid that has many consumer and industrial applications. Decamethylcyclopentasiloxane is used as an ingredient in a number of personal-care and beauty products, including deodorants, antiperspirants, cosmetics, shampoos, and body lotions. It is also used as a drycleaning solvent and an industrial cleaner.

There is concern about potential toxicity and transport into the environment, and consequently, and therefore a number of cyclic siloxanes are currently under review for priority pollutant classification in North America and Europe [302]. They have been previously measured in wastewater, river water, and landfill

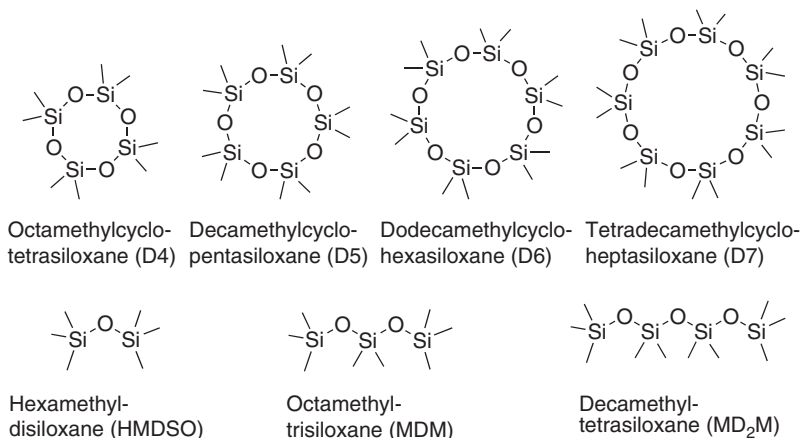


Figure 9.13 Structure of the most common siloxanes (cyclic and linear).

biogases. Sanchis *et al.* [302] published a new GC–MS/MS method that enables the measurement both of cyclic siloxanes and of linear methylsiloxanes in a single method for natural waters, wastewater, and sediments. The quantification limits ranged from 2.7 to 7.5 ng L⁻¹ for cyclic siloxanes and 0.5 to 1.4 for linear methylsiloxanes in wastewater. Bletsou *et al.* [303] examined the mass loading and fate of 12 linear and 5 cyclic siloxanes in a wastewater-treatment plant in Greece.

Toxicological studies on decamethylcyclopentasiloxane and several other siloxanes are being conducted voluntarily by the Dow Corning Corporation under a Memorandum of Understanding signed in 1996 with EPA. In 2005, EPA received the final results of the two-year study in rats, which confirmed the significant increase in uterine tumors following exposure to 160 ppm of decamethylcyclopentasiloxane, the highest concentration tested in the study. No significant increase in tumors was detected at lower doses.

9.11.2 1,4-Dioxane

1,4-Dioxane is a synthetic industrial chemical that is completely miscible in water [304]. Unstable at high temperatures and pressures, 1,4-dioxane is potentially explosive if exposed to light or air. It is used as a stabilizer for chlorinated solvents such as 1,1,1-trichloroethane (TCA), a solvent for impregnating cellulose acetate membrane filters, a wetting and dispersing agent in textile processes, and as a laboratory cryoscopic solvent for molecular mass determinations. It is used in many products, including paint strippers, dyes, greases, varnishes, and waxes. It is also a by-product in the manufacture of polyethylene terephthalate (PET) plastic and is used as a purifying agent in the manufacture of PCs. 1,4-Dioxane is also found as an impurity in antifreeze and aircraft deicing fluids and in some consumer products (deodorants, shampoos, and cosmetics) [304].

1,4-Dioxane is a likely contaminant at many federal facilities because of its widespread use. Residues may be present in manufactured food additives, 1,4-dioxane-containing food-packaging materials, or in food crops treated with pesticides that contain 1,4-dioxane (such as vine-ripened tomatoes). No drinking-water standards have been established for this compound.

9.11.3 Nitroaromatic Compounds

The production of nitroaromatic compounds is one of the largest chemical industrial activities today. These compounds are used in explosives, as starting materials in the pesticide and pharmaceutical industries, and in dyes, among many other applications. They are identified by one or more functional nitro groups attached to the aromatic ring structure. Many synthetic nitroaromatic compounds have been identified as toxic, mutagenic, carcinogenic, and persistent against degradation [305].

The most famous explosive is trinitrotoluene (TNT), which was used mainly in warfare in both world wars, as well as in mining and building. TNT is still widely used and produced. Most of the current problems with TNT and nitroarene compounds are found at sites where ammunition was handled, stored or manufactured. TNT is a persistent contaminant, but its microbial degradation is possible both aerobically [306] and anerobically [307].

Although some nitroaromatic compounds are purposefully spread in the environment as pesticides, the majority of their environmental releases are accidental. For example, in the United States alone, 5.1 t of nitrobenzene was released in soil in 2002 [308]. The greatest known industrial releases have occurred in China; in 2005, an explosion at a chemical factory resulted in the accidental release of 100 t of benzene and nitrobenzene into the Songhua River.

9.11.3.1 2,4-Dinitrophenol

The 2,4-dinitrophenol was used in the manufacture of munitions during the World War I [309, 310]. Since then, it has also been used as a dye, wood preserver, herbicide, and photographic developer.

In 1933, Tainter discovered that the human consumption of 2,4-dinitrophenol led to significant weight loss and soon it was popularized as a weight loss drug [311].

The UK Food Standard Agency issued a warning in 2003, labeling 2,4-dinitrophenol as “not fit for human consumption.” This warning was aimed specifically at bodybuilders, to avoid its use due to significant potential for short-term and long-term harm, following the hospitalization of a Finnish bodybuilder after having taken DNP.²⁶

9.11.4 Naphthenic Acids

Naphthenic acids are a complex mixture of alkyl-substituted acyclic and cycloaliphatic carboxylic acids that dissolve in water at neutral or alkaline pH and have surfactant-like properties. They occur naturally in crude-oil deposits worldwide (up to 4% by weight) and have also been recently discovered in coal, which could be a source of contamination for groundwater. Naphthenic acids are toxic to aquatic organisms, including phytoplankton, daphnia, fish, and mammals, and are also endocrine disrupting.

Caustic hot water is used in the extraction of crude oil from oilsands, which results in residual tailing water (0.1–0.2 m³ of tailings per tonne of oil-sands processed) that contains high levels of naphthenic acids (80–120 mg L⁻¹ levels are common) and is very toxic.

9.11.5 Other Chlorinated Compounds

Chlorinated compounds have been and still are produced for many purposes. PVC production is the most important reason for synthetic organochlorides. The manufacture of the precursor for the plastic, vinyl chloride, is the main reason for dioxin pollution in the United States. The USEPA lists accidental fires and burning of municipal waste containing PVC plastic as other major sources of dioxins. Dioxins are slowly degradable and tend to accumulate in sediments.

Another important source of organochloride production is the dry-cleaning industry, where the main compound used is TCE. Although the use of TCE has

²⁶ Food Standard Agency (2011) Food Standards Agency issues urgent advice on consumption of “fat burner” capsules containing DNP. <http://www.food.gov.uk/news/pressreleases/2003/jun/fatburnpress>.

declined throughout the 1990s due to its classification as a hazardous compound by the USEPA, it is still used in dry-cleaning facilities. For example, in 2001, US plants produced approximately 148 million kg of TCE [312].

Of the 16 POPs listed in the 1998 Aarhus Protocol,²⁷ 11 are organochloride pesticides, which have now been banned in several countries. The most famous example of this is DDT, which was first synthesized in the 1940s. DDT has been banned in many countries, but totally phasing out its use is difficult because it is efficient in preventing malaria vectors, and it is still produced at 4–5 t yr⁻¹ [313].

Organochlorides of low molecular mass are readily water-soluble and thus can easily contaminate groundwater. Due to the hydrophilic nature of the chlorine atom, organochlorides are efficient compounds in cleaning agents. TCE is used by 90% of dry-cleaners in the United States today. It is toxic to humans and is a suspected carcinogen.

Dioxins are a large group of very toxic chemicals formed when organic matter is burned in the presence of chlorine. Polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) are among the most thoroughly studied dioxins. Certain dioxins have in fact been coined as the most toxic compounds ever made by humans. Dioxins found contaminating the environment are largely the result of human activity. The highest concentrations of dioxins are often found in soils and sediments near the facilities where they are produced or used. Currently, the largest source of dioxins is the incineration of chlorine-containing waste, which creates dioxin air pollution. Dioxins are lipophilic compounds that tend to accumulate in the adipose tissues of higher organisms. Dioxins are also found as impurities in PCB products or wood preservatives. A group of dioxins called chlorophenol herbicides, such as 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), are commercially produced in large quantities.

Chlorinated phenols have been traditionally applied in the production of wood preservatives, insecticides, and disinfectants. Common chlorinated phenols found in wood preservatives are 2,3,4,6-tetrachlorophenol (TeCP), 2,4,6-trichlorophenol (TCP), and pentachlorophenol (PCP), in order of abundance.

9.11.6 Perchlorate

Perchlorate has been used in solid propellants used for rockets, missiles, and fireworks as well as in highway flares, safety matches, and airbag inflation systems. There is also potential contamination from fertilizers (e.g., Chilean nitrate, where perchlorate co-occurs naturally), and recent work has revealed other natural sources of perchlorate. In addition, perchlorate can be a contaminant in sodium hypochlorite (liquid bleach) that is used in drinking water treatment.

Perchlorate has been designated as an important environmental contaminant following its discovery in a number of water supplies in the western United States. It has since been found in environmental waters across the United States and in other parts of the world at $\mu\text{g L}^{-1}$ levels. For example, a fireworks and

²⁷ http://www.unece.org/env/lrtap/pops_h1.html.

safety-match manufacturing area in India was investigated by Isobe *et al.* [314] as a source of perchlorate contamination as well as in fresh produce, foods, wines, and beverages from many countries, including those in Europe and the Far East. Perchlorate has also been found in biological samples. Health concerns arise from the ability of perchlorate to displace iodide in the thyroid gland, which can affect metabolism, growth, and development.

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10

Surfactants in the Environment

10.1 Introduction

According to the IUPAC, a surfactant is a substance that lowers the surface tension of the medium in which it is dissolved, and/or the interfacial tension with other phases, and, accordingly, is positively adsorbed at the liquid/vapor and/or at other interfaces.¹

Surface Active Agents (SurfActAnts) are organic chemicals that reduce surface tension in water and other liquids. The most familiar use for surfactants is in the manufacture of soaps, laundry detergents, dishwashing liquids and shampoos. Other important uses are in the many industrial applications for surfactants in lubricants, emulsion polymerization, textile processing, mining flocculants, petroleum recovery, wastewater treatment, pesticide application, and many other products and processes. Surfactants are also used as dispersants after oil spills.

Most compounds used as surfactants are amphiphilic organic molecules, containing two well-defined and differentiated parts incorporated into the same structure. The first is a hydrophilic group termed the head, and the second one is a hydrophobic agrupation, called the tail. Thus, surfactants show both an apolar water-insoluble moiety and a polar water-soluble moiety.

Surfactants are able to diffuse in water and adsorb at the interfaces between air and water or at the interface between nonpolar molecules and water. In the case where water is mixed with insoluble materials, for example oils or hydrocarbons, the corresponding water-insoluble hydrophobic agrupation, the tail, may extend out of the bulk water phase into the air or into the water-insoluble phase, while the water-soluble head group remains in the water phase.

In the aqueous phase, surfactants form aggregates dispersed into the liquid yielding colloids, where the hydrophobic tails form the core of the aggregate and the hydrophilic heads remain in contact with the surrounding liquid. Such aggregates show spherical or cylindrical shapes (micelles), or form structures composed of two molecular aggregates with polar head groups pointing to the water (bilayers) (see Figure 10.1).

The shapes of these micelles depend basically on the chemical structure of each surfactant, according to the balance in size between the hydrophilic head and hydrophobic tail.

1 <http://goldbook.iupac.org/S06194.html>.

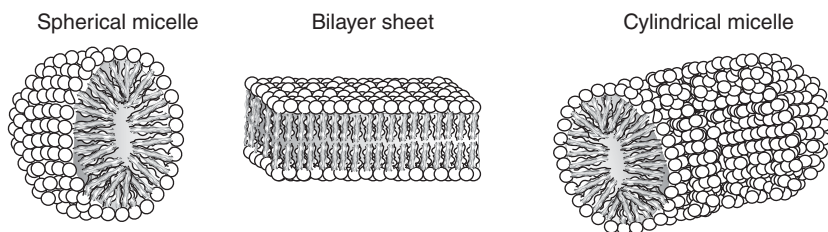


Figure 10.1 Most commonly observed geometrical shapes of surfactant micelles in aqueous solution.

10.2 Structure and Classification

Surfactants can be classified according to their chemical structure. Surfactant molecules have either one tail or two; those with two tails are said to be double-chained. The most common structures of the tail of most surfactants are fairly similar, consisting of an apolar carbon chain, which can be linear or branched, or some aromatic rings, but in others some variations can be found, for example, as in fluorosurfactants (fluorocarbon chains) or siloxane surfactants (siloxane chains) (see Figure 10.2).

Many surfactants include a polyether chain terminating in a highly polar anionic group. The polyether groups often include several proportions of ethoxylated (polyethylene oxide-like) sequences inserted into the chain to increase the hydrophilic character of a surfactant and polypropylene oxides conversely to increase the lipophilic character. Most commonly, surfactants are classified according to the polar head group as nonionic, anionic, cationic, and amphoteric (zwitterionic) (see Figure 10.3).

Some examples of common commercial surfactants are shown in Table 10.1, together with the specific properties of each.

The annual worldwide use of surfactants has been steadily increasing. A brief summary of the surfactant sales in the EU in 2014 is shown in Figure 10.4.

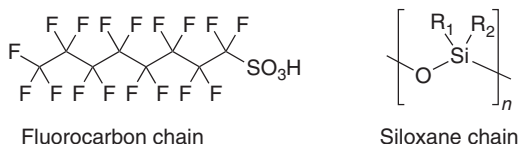


Figure 10.2 Structure of the tail in surfactants.

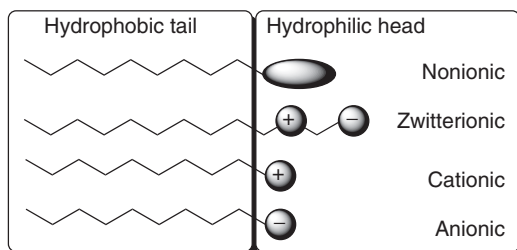
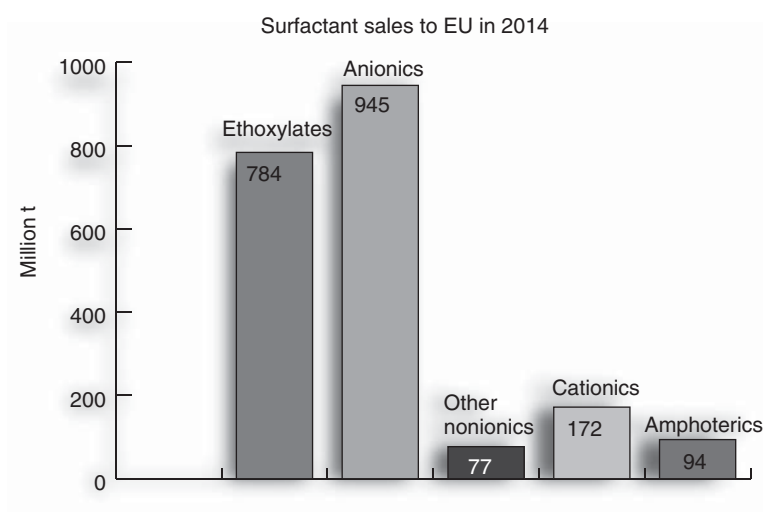


Figure 10.3 Scheme of the head type in surfactants.

Table 10.1 Some examples of major commercial and industrial surfactants.^{a)}

Type/use	Commercial and domestic examples	Major industrial examples
Anionic	Sodium linear alkylbenzene sulfonate (LABS); sodium lauryl sulfate; sodium lauryl ether sulfates	Petroleum sulfonates; linosulfonates; naphthalene sulfonates, branched alkylbenzene sulfonates; linear alkylbenzene sulfonates; alcohol sulfates
Cationic	Stearalkonium chloride; benzalkonium chloride	Quaternary ammonium compounds; amine compounds
Nonionic	Dodecyl dimethylamine oxide; coco diethanol-amide alcohol ethoxylates; linear primary alcohol polyethoxylate	Alkylphenol ethoxylates; alcohol ethoxylates; EO/PO polyol block polymers; polyethylene glycol esters; fatty acid alkanolamides
Amphoteric	Cocoamphocarboxyglycinate; cocamidopropylbetaine	Betaines; imidazolines

a) Data taken from Ref. [1].

**Figure 10.4** Surfactant sales in the EU in 2014.²

10.3 Nonionic Surfactants

A nonionic surfactant has no charged groups in its head. They are constituted by hydrophilic polar groups such as alcohols, phenols, ethers, esters, or amides that do not ionize in aqueous solution. Many of these nonionic surfactants present a

² Data taken from European Committee of Surfactants and their Organic Intermediates (CESIO), Statistics. <http://www.cefic.be/cesio>, 2014.

hydrophilic part formed by chains such as polyethylene glycol chains, produced by the polycondensation of ethylene oxide (termed polyethoxylated nonionic surfactants). The most abundant nonionic surfactants in use are alcohol ethoxylates (AEOs) and alkylphenol ethoxylates (APEOs) [2].

In the 1990s, polar-sugar-based head groups were introduced in the market, because of their low environmental impact and null toxicity. As far as the lipophilic group is concerned, it is often an alkyl or alkyl benzene type, the former coming from fatty acids of natural origin. The polycondensation of propylene oxide produces a polyether which (as opposed to polyethylene oxide) is slightly hydrophobic. This polyether chain is used as the lipophilic group in the so-called polyEOpolyPO block copolymers, which are most often included in a different class, that is, polymeric surfactants.

10.3.1 Fatty Alcohols

Fatty alcohols that have been used primarily as co-emulsifiers belong to this group. Fatty alcohol ethoxylates (FAEs) represent the economically most remarkable group of nonionic surfactants (see Figure 10.5). Commercial FAEs generally consist of a mixture of several homologs differing in the alkyl chain length of the fatty alcohol and degree of ethoxylation.

The influence of the fatty alcohol chain length on the properties of the compound is small compared to that of the polyoxyethylene chain. Many emulsifiers, wetting agents, and solubilizers are based on fatty alcohols and can be found in domestic and commercial detergents, household cleaners, and PCPs. Thus, the most common route of disposal of FAEs is down the drain, through sewage systems, and into municipal WWTPs [3].

10.3.2 Alcohol Ethoxylates

AEOs are by far the most commonly used substitutes for nonylphenol ethoxylates (NPEOs) in Europe [4]. AEOs are also employed in pesticide formulations and as spray adjuvants [5]. AEOs are used as technical mixtures, so they are not one single compound but a mixture of isomers [6]. The alkyl chain of AEOs usually has C_2 – C_{16} and between 7 and 15 EO units (see Figure 10.6).

The AEOs and NPEOs exhibit a similar range of toxicity to aquatic organisms. Unlike NPEOs, biodegradation intermediates of AEOs are less toxic than those of the parent surfactants [4]. Although several studies show that these compounds can persist after biological treatment [4], AEOs are largely degraded during

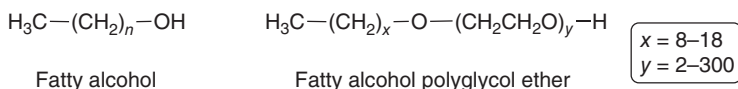


Figure 10.5 General formula of fatty alcohol polyglycol ethers.

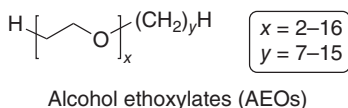


Figure 10.6 Chemical structure of an AEO nonionic surfactant.

sewage treatment, suggesting that biodegradation is responsible for most of the removal observed [6].

10.3.3 Ethylene Oxide/Propylene Oxide-Block Polymers

These surfactants consist of a central polypropylene glycol (PPG) moiety representing the hydrophobic portion of the molecule and two hydrophilic polyethylene glycol (PEG) chains. They are also called EO/PO block polymers. Depending on the molecular weight and the ratio between the PPG and PEG a wide variety of surface active agents can be designed. EO/PO block polymers are used in dishwashing and laundry detergents (see Figure 10.7). They display thickening and gelling properties, which make them useful in cosmetics preparations. In the pharmaceutical field, the more hydrophilic types are used as solubilizers under the name poloxamer.

10.3.4 Alkylphenol Ethoxylates

APEOs³ (see Figure 10.8) are nonionic surfactants that have been used since the 1940s as detergents and emulsifiers in domestic, industrial, and institutional applications, including paper production, leather and textile processing, and cleaning products. APEOs have also been used as an adjuvant in some pesticide formulations [7]. They may be used as wetting and washing agents as well as emulsifiers and solubilizers. In APEOs, the number of EO units is between 1 and 23, while the alkyl chain can be either 8 or 9 units in length and are known as octylphenol ethoxylates (OPEOs) or NPEOs [8].

4-NP is used to produce NPEOs, because of their ability to be resistant to biodegradation at low temperatures. However, the use of NPEO is diminishing (see Figure 10.9) because of the generation of some persistent metabolites during the degradation process, which are much more toxic than the original compound [9]. Moreover, these chemicals have been banned in domestic formulations in

Figure 10.7 Structure of EO/PO block polymers.

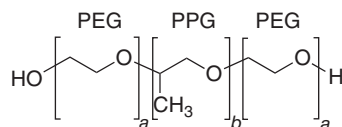
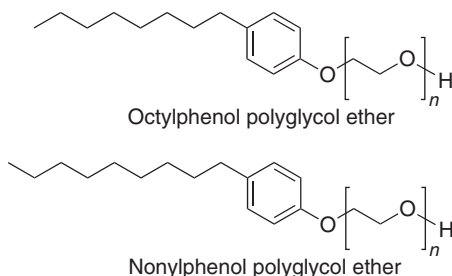


Figure 10.8 Structure of two major alkylphenol polyglycol ethers.



³ Also known as alkylphenol polyglycol ethers.

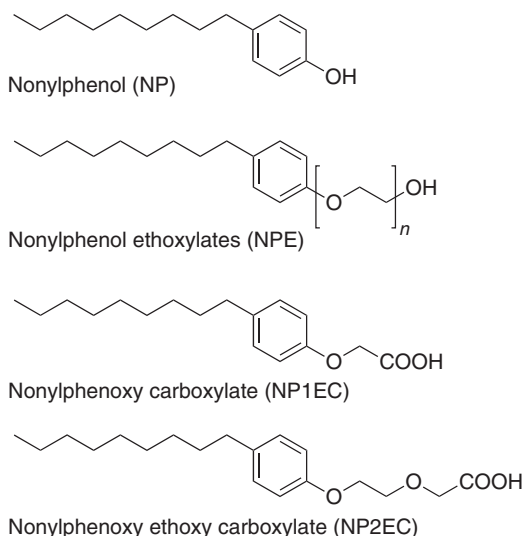


Figure 10.9 Structure of 4-NP and its derivatives.

some countries of the EU (Germany, Spain, and the United Kingdom) [10], as well as in Switzerland and Canada [11].

10.3.5 Ethoxylated Oils and Fats

These surfactants are ethoxylated derivatives of lanolin (wool fat) and castor oil. The name lanolin is applied to a wax containing a complex mixture of esters and polyesters of high-molecular-weight alcohols (aliphatic, steroid, and triterpenoid) and fatty acids (saturated, unsaturated, hydroxylated, and non-hydroxylated). Castor oil is a mixture from cold pressing of castorbean (*Ricinus communis*) seeds, formed by a mixture of a triglyceride of fatty acids.⁴ These ethoxylated mixtures of lanolin and castor oil are good emulsifiers and solubilizers, respectively. Both are used mainly in the cosmetics industry and the castor-oil-based products are solubilizers for pharmaceutical purposes.

10.3.6 Alkanolamides

The main family of this group includes *N*-acyl derivatives of monoethanolamine and diethanolamine (see Figure 10.10). They have been used as foams, foam boosters, and foam stabilizers in household detergent products, shampoos, and cleaners.

The second family of this group is composed of ethoxylated alkanolamides produced by the reaction of an alkanolamide with ethylene oxide to give an ethoxylated amide (see Figure 10.10). Their properties are very similar to those of ethoxylated alcohols. They are used for thickening, foam stabilizing, and dispersing substances as well as in car-wash products.

⁴ Composed by ricinoleic 87.5%, oleic 5%, linoleic 4%, palmitic 1.5%, linolenic 0.5%, stearic 0.5%, dihydroxystearic 0.5%, and arachidic 0.5% acids.

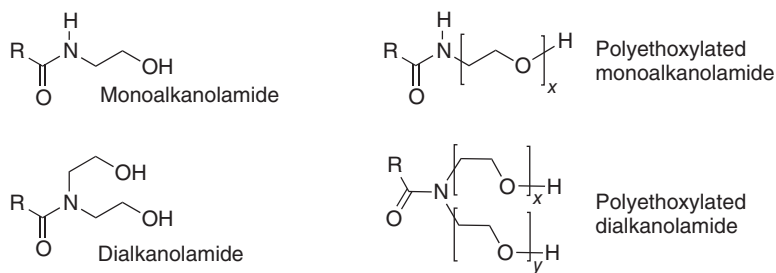
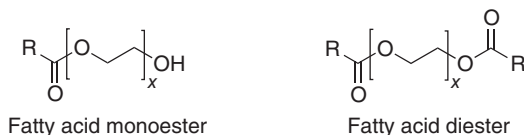


Figure 10.10 Structure of alkanolamides.

Figure 10.11 Structure of ethoxylated fatty acids.



10.3.7 Esters

Esters derived from fatty acids constitute another remarkable family of products that are used as nonionic surfactants. Outstanding in this group are ethoxylated fatty acids and fatty acid monoesters and diesters derived from polyethylene glycol (see Figure 10.11). When ethylene oxide reacts with a fatty acid, a mixture of monoesters, diesters, and unreacted fatty acid with a broad x value results.

Monoesters are much more soluble in water than are diesters. These surfactants are readily hydrolyzed under acidic or alkaline conditions. Such fatty acid esters are excellent emulsifiers used for cosmetic, household, and industrial preparations. Adequate combinations of these esters with low and high degrees of ethoxylation provide excellent emulsifying properties for creams and lotions used in cosmetic or pharmaceutical formulations. Like any ester derivative, these surfactants can be hydrolyzed under acidic or alkaline conditions.

10.3.8 Nonionic Surfactants Derived from Carbohydrates and Related Compounds

Carbohydrate-based surfactants have become a class of surfactants of growing interest because they have been proved to be highly affordable and environmentally advantageous. They are the result of a combination of a sugar derivative or related compounds with a fatty moiety, which can be prepared synthetically or by biotechnological methods (see Figure 10.12) [12].

The esters of fatty acids and glycol or glycerol are lipophilic surfactants showing a hydrophilic-lipophilic balance (HLB) value below 10.

Due to their very low toxicity, these surfactants are edible and, therefore, they are widely used in the food industry, especially in applications involving water-in-oil emulsions or dispersions (e.g., butter, diet butter, margarine). Glycol and glycerol esters are also used in the pharmaceutical and cosmetic industry either as emulsifying agents or as oily compounds in creams, lotions, ointments, and gels.

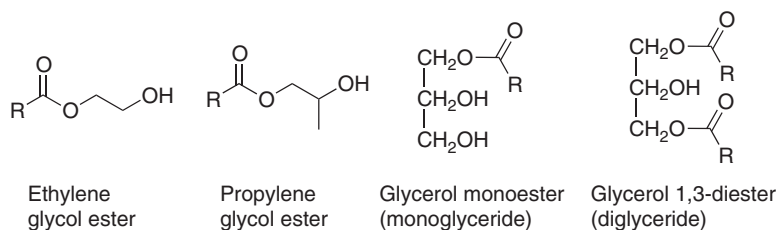


Figure 10.12 Chemical structure of glycol and glycerol esters.

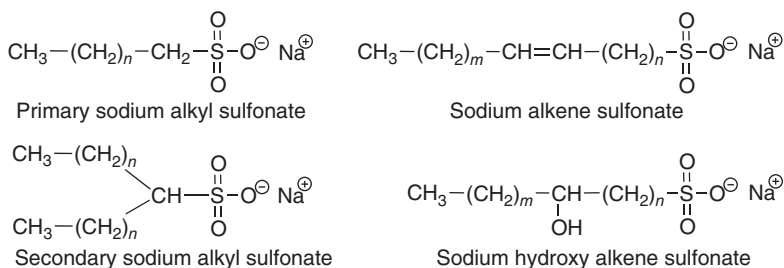


Figure 10.13 Structure of alkyl polyglucosides.

10.3.8.1 Alkyl Polyglucosides

The alkyl polyglucosides belong to nonionic surfactants of growing use. They are prepared from renewable raw materials, namely (starch/sugar) and fatty alcohols (vegetable oils) (see Figure 10.13). As these chemicals belong to a new type of surfactants, only few studies have addressed their environmental properties [13].

Because of their good foaming properties, as well as synergy with other surfactants, they have been applied in the manufacture of dishwashing and laundry detergents and in other cleaning products [14]. Further, their good skin tolerance makes them suitable for mild personal-care products [15].

The numerous hydroxyls present in glucoside groups ensure the solubility of the whole molecule in water. Alkyl polyglucosides show good water solubility and have their cloud points at rather high temperatures (generally above 100°C); in addition, they are only slightly sensitive to the presence of electrolytes and are only rarely influenced by water hardness. It is observed that an alkyl polyglucoside achieves optimal detergency with an average alkyl chain length of around 13 and a glucosidic content of about 65%. Alkyl polyglucosides show good chemical stability at neutral and alkaline pH.

10.3.8.2 Sorbitan Esters

Sorbitol can form two different sorbitans by internal dehydration: 1,4- and 1,5-sorbitan. Further dehydration of 1,4-sorbitan leads to isosorbide. In common sorbitan-based surfactants 1,4-sorbitan is predominant. Fatty acid esters of sorbitan are insoluble in water, their HLB value is below 10. Figure 10.14 depicts the chemical structure of the basic compounds. These compounds are used as emulsifiers often in combination with ethoxylated sorbitan esters of fatty acids.

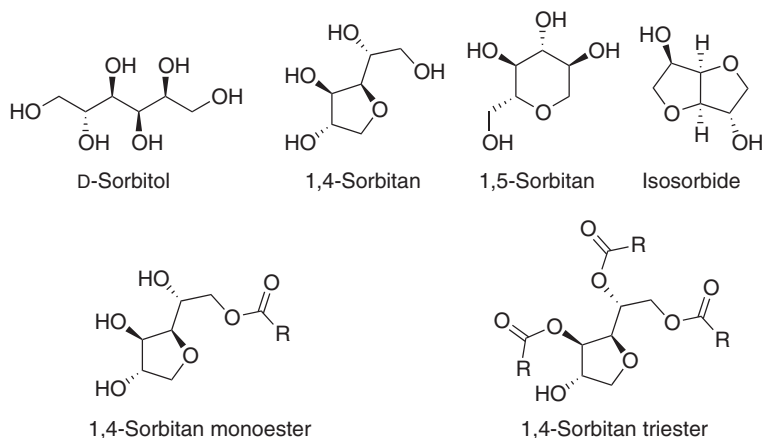
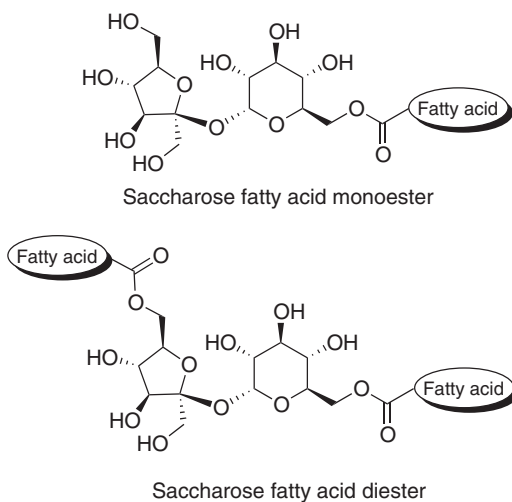


Figure 10.14 Structure of sorbitans and their ester-based emulsifiers.

Figure 10.15 Chemical structure of sucrose esters.



10.3.8.3 Alkyl Carbohydrate Esters

Alkyl carbohydrate esters are also known under the names “sugar esters” and “sucrose esters.” Normally, they are based on saccharose (see Figure 10.15). Mono- and diesters are produced. The monoesters are water soluble while the diesters are not. Due to the steric effects, primary hydroxyl groups are almost exclusively subject to esterification. They are of great interest due to their natural origin of their components and good biodegradability. Sucrose esters are food-grade ingredients and have similar food additive uses, as previously described for glycol, glycerol, and sorbitan esters.

10.3.9 Ester/Ether Surfactants

Besides the ester group (which is formed by a fatty acid and a polyol as described in the previous section), these surfactants contain ether linkages that normally

originate from polyoxyethylene. In general, they are more hydrophilic compared to the ester surfactants and exhibit HLB values above 10.

10.3.9.1 Ethoxylated Glycol and Glycerol Esters

In addition to monoesters, diesters are possible mainly in the case of glycerol (see Figure 10.16). Emulsifiers are used for oil-in-water emulsions in cosmetics and pharmaceuticals.

10.3.9.2 Ethoxylated Sorbitan Esters

Ethoxylation of sorbitan fatty acid esters leads to an important surfactant class used in the pharmaceutical and cosmetic industry. The fatty acids used are lauric, myristic, palmitic, stearic, and oleic acid (see Figure 10.17). Emulsifiers are used for cosmetic and pharmaceutical emulsions, and solubilizers for oily liquids such as vitamins and hormones. They are wetting agents in suspensions.

10.3.9.3 Ethoxylated Pentaerythritol Esters

They are used as emulsifiers for cosmetic preparations. Their chemical structures are depicted in Figure 10.18.

10.3.9.4 Polyglycerol Monoester

This is the only class of ether bonds containing emulsifiers that do not contain polyoxyethylene groups. The ether linkage is formed from glycerol units (see Figure 10.19).

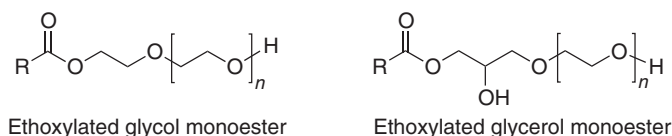


Figure 10.16 Chemical structure of glycol and glycerol esters.

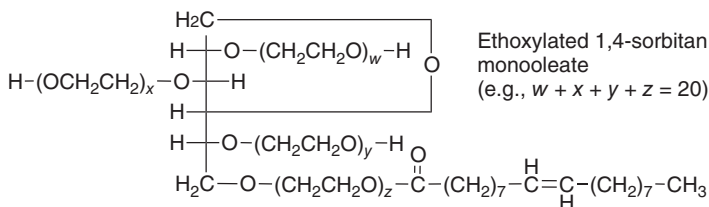


Figure 10.17 Chemical structure of ethoxylated sorbitan fatty acid esters.

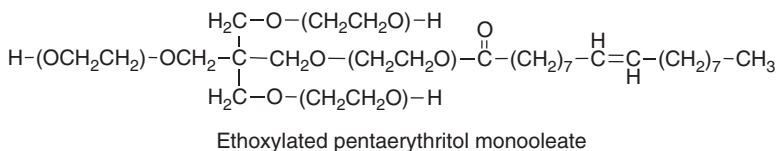


Figure 10.18 Chemical structure of ethoxylated pentaerythritol ester.

Figure 10.19 Chemical structure of polyglycerol monooleate.

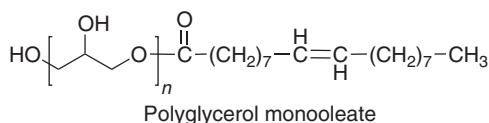
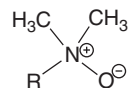


Figure 10.20 Chemical structure of alkyl dimethylamine oxide.



10.3.10 Amine Oxides

Amine-oxide-based surfactants constitute a particular type of nonionic surfactants; they are classified as nitrogen nonionic surfactants, exhibit cationic behavior in acid solution, and can be ionized depending on the pH of the test medium (see Figure 10.20).

Amine oxides are produced from alkyl dimethyl amine, where the alkyl chain is a C_{12} – C_{18} unit by oxidation. The methyl groups could be partially replaced by other functional groups such as amidopropyl, hydroxyethyl, or hydroxypropyl.

Amine oxides contribute to impart viscosity, show good foaming properties and are skin compatible [16]. These compounds are widely used in shampoos, detergents, toiletries, and antistatic preparations (liquid bleach products, textile industry, foam stabilizers, and anti-corrosion formulations), usually in combination with other surfactants. They are compatible with anionic surfactants and can be used to give synergistic advantages to formulations. They are especially suitable in slightly acidic or neutral formulas.

10.4 Anionic Surfactants

Anionic surfactants contain functional groups at their head, and are capable of forming anions. They dissociate in water into an amphiphilic anion and a cation, which are formed, generally, by an alkaline metal (Na^+ , K^+) or a quaternary ammonium salt. The most commonly used anion is a carboxylate moiety, although the following anionic groups can also be used for such surfactants. Linear alkylbenzene sulfonate (LAS), alkyl ethoxysulfates (AES), and alkyl sulfates (AS) comprise the largest volume of anionic surfactants.

10.4.1 Carboxylic Acids Derivatives

10.4.1.1 Carboxylic Acid Salts

Fatty acids are easily transformed into alkali and short-chain amine salts such as ethanol amine, diethanol amine, and triethanol amine. They show good water affinity and are widely used for hand-washing soaps, prepared generally from tallow/coconut oil mixtures. These water-soluble soaps are used mainly in cosmetic preparations as skin cleansers, traditional soap bars, and liquids soaps. They are also used in shaving sticks, foams, or creams, and deodorant sticks. In nonaqueous systems, water-insoluble soaps form gels and, due to their hydrophobicity, they can be appropriate surfactants or thickeners for water/octanol emulsions.

Some of them are used as lubricants in the polymer industry, for example, magnesium stearate.

Monoesters of di- and tricarboxylic acids are synthesized by condensation reactions from different types of molecules: either an alcohol with a polycarboxylic acid (e.g., tartaric or citric acid), or an hydroxy acid (e.g., lactic acid or citric acid) with a carboxylic acid. The alcohol may have been previously ethoxylated to enhance water solubility and surface activity (see Figure 10.21).

Such surfactants have excellent foaming properties and substantivity on the hair. Ester carboxylates are commonly present in shampoo formulations in combination with alcohol ethoxy sulfates because they are capable of reducing skin irritation.

10.4.1.2 Ether Carboxylic Acids

Another group of ether carboxylic acids are usually formed by the reaction of sodium chloroacetate with ethoxylated alcohols. Due to the addition of ethoxylated groups, ether carboxylates (see Figure 10.22) are more soluble in water and less sensitive to water hardness compared to conventional soaps. Ether carboxylates do not undergo hydrolysis in the presence of weak alkalis or acids.

These anionic surfactants improve the foaming quality of the detergent, reducing the irritation level, and therefore they are used as co-surfactants in detergents that have to be in contact with the skin [17]. These surfactants are marketed in concentrated acid form. For these products, aerobic biodegradation employing standardized methods has been studied, which uses microorganism to degrade the surfactant [18].

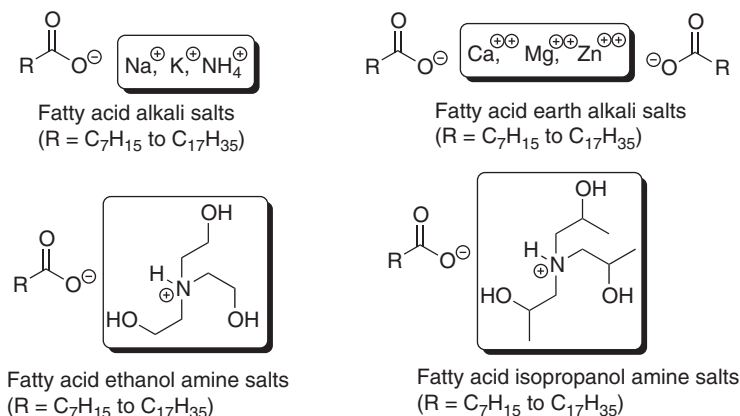


Figure 10.21 Structure of carboxylic acid derivatives salts.

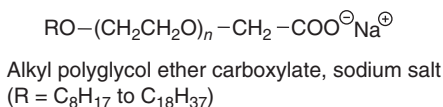
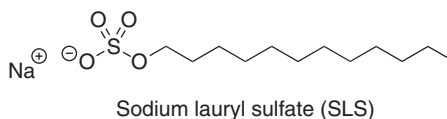


Figure 10.22 Chemical structure of an ether carboxylate salt.

Figure 10.23 Chemical structure of sodium lauryl sulfate (SLS).



10.4.2 Sulfuric and Sulfonic Acid Derivatives

10.4.2.1 Alkyl Sulfates

Alkyl sulfates are organic esters of sulfuric acid; the sulfur atom is bridged to the carbon atom of the hydrocarbon chain via an oxygen atom. Sodium lauryl sulfate, one of the most common surfactants, belongs to this class (see Figure 10.23). Alkyl sulfates have, for many years, been the most important synthetic surfactant. As foamers and emulsifiers, they are still used in cosmetics and personal-care products. They are also used in combination with other surfactants to improve the foaming characteristics of detergent systems. Pure sodium lauryl sulfate is used in oral care and incorporated in dental creams.

The second most abundant surfactants in the group of anionic surfactants are alkyl ethoxy sulfates (AEOSs) (see Figure 10.24). Alkyl ether sulfates (AES), which are also called alcohol ethoxy sulfates (AEOS), result from the sulfation of an ethoxylated alcohol. These compounds have an alkyl chain length of C_{12} – C_{16} and a chain of 3 or 4 ethylene oxide (EO) units, on average (see Figure 10.6) [19].

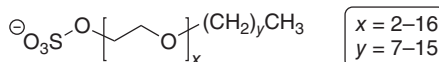
Alkyl ether sulfates are used as household cleaners (e.g., carpet cleaners), in dishwashing liquids, and fabric care products (powders and liquids), and in PCPs such as liquid soaps, shower gels, foam baths, and, especially, shampoos. Increasing the ethoxylation degree reduces skin and eye irritation. They are generally combined with other nonionic or anionic surfactants. In contrast to alkyl sulfates in alkyl sulfonates the sulfur atom is directly linked to the carbon atom making the substances stable against hydrolysis.

10.4.2.2 Alkyl Sulfonates

Three major types of alkyl sulfonates must be considered: the primary and secondary paraffin sulfonates (PS and SAS) and the α -olefin sulfonates (AOS) (see Figure 10.25). Alkane sulfonates (PS and SAS) are highly water soluble, showing good foaming, wetting, and emulsifying properties. They are used mainly in Europe in heavy- and light-duty powder detergents as well as in all-purpose hard-surface liquid cleaners. Due to their excellent resistance to high electrolyte contents, alkane sulfonates are also promising as concentrated industrial or domestic cleaners containing mineral chemical additives.

α -Olefin sulfonates (AOSs) have been used mainly in Asia as surfactants for heavy- and light-duty laundry detergents, synthetic soap bars, and household products; they have also been used in the United States in several PCPs (liquid

Figure 10.24 Chemical structure of alcohol ethoxy sulfates (AEOSs) anionic surfactants.



Alcohol ethoxy sulfates (AEOSs)
Alkyl ether sulfates (AESs)

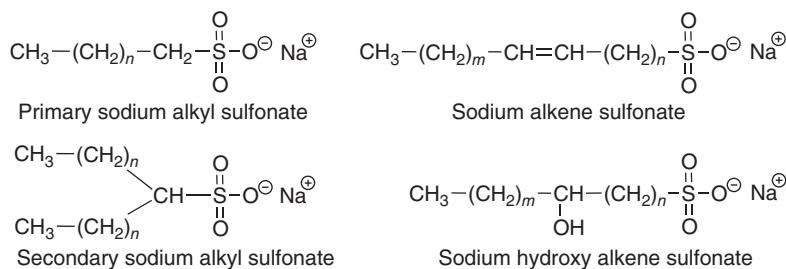


Figure 10.25 Chemical structure of alkyl sulfonates.

soaps, bubble baths, and shampoos) as alternatives to alcohol ether sulfates. They are also marginally used in oral-care formulations.

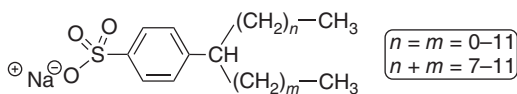
10.4.2.3 Alkylbenzene Sulfonates

LASs are the most widely used synthetic anionic surfactants. They have been extensively used for over 50 years and they have emerged as the dominant precursor of biodegradable detergents [20]. LASs are commercially available, especially in household detergents and surface cleaners, as a mixture of homologs having C_9 – C_{15} in their alkyl chain and isomers resulting from the different attachment positions of the phenyl group along that chain (see Figure 10.26) [21].

Biodegradable, LASs exhibit good chemical and thermal stability and can be incorporated in spray-dried slurries. LASs are very cost-effective surfactants that are used in the manufacture of a broad variety of detergents for household, fabric care, institutional, and industrial use. In laundry products (powders and liquids), LAS is the surfactant of choice, usually used in combination with other anionic or nonionic surfactants. LAS is also an appropriate anionic surfactant for light-duty and delicate powder laundry detergents. LASs are well known in hand dishwashing formulations, often in combination with AEOS (i.e. alcohol ethoxy sulfate), providing better foam resistance. Due to its strong detergative action, LAS has a low compatibility with skin and is scarcely used in cosmetics, except in antiseborrheic preparations.

10.4.2.4 Sulfosuccinates

Sulfosuccinates are the sodium salts of alkyl esters of sulfosuccinic acid; monoesters of sulfosuccinic acid based on linear fatty alcohols are only partially water-soluble and hardly dispersible (see Figure 10.27). Those based on fatty alcohol ethoxylates exhibit much better solubility. Dialkyl esters based on alcohols with less than nine carbons, preferably five to eight carbon atoms, as well as those based on fatty acid ethanol amides are water soluble and, therefore, are generally preferred. Disodium salts of monoesters show good detergency



Sodium alkylbenzene sulfonate (LAS)

Figure 10.26 Chemical structure of sodium alkylbenzene sulfonates (LAS).

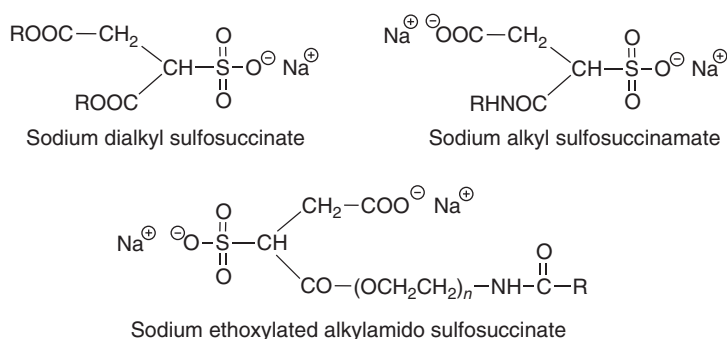


Figure 10.27 Chemical structure of sulfosuccinates.

and foam properties. Due to the ester linkage, all sulfosuccinates are sensitive to hydrolysis, especially under acidic conditions.

The monoesters of alkanolamides and their derivatives are extensively used in PCPs, especially in shampoos, often in combination with other anionic surfactants. The diesters are used as dispersing and wetting agents in industrial or institutional applications such as emulsion polymerization, the textile industry, ink manufacture, dry cleaning, and agriculture.

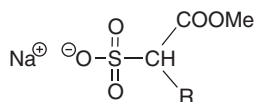
10.4.2.5 Sulfo Fatty Acid Esters

Among this group of surfactants the α -sulfo fatty acid esters are commonly used on an industrial scale. The α -sulfo fatty acid esters contain the sulfonate group statistically distributed along the carboxylate chain (see Figure 10.28). α -Sulfo methyl ester surfactants deriving from C_{16} – C_{18} fatty acid are used in phosphate-free laundry detergents.

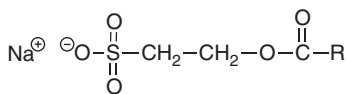
10.4.2.6 Fatty Acid Isethionates and Taurides

Taurides (or taurates) are acylamino alkane sulfonates that have chemical structures close to isethionates (see Figure 10.29). These surfactants are insensitive to water hardness and show good wetting, foaming, and emulsifying properties. In addition, they have excellent compatibility with the skin. Acyl isethionates have been used in shampoos and personal cleaners. They are also incorporated in syndet bars, together with various soaps.

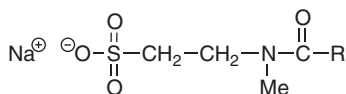
Figure 10.28 Chemical structure of sulfo fatty acid esters.



Alkyl ester of α -sulfo fatty acid sodium salt



Fatty acid isethionate



Tauride

Figure 10.29 Chemical structure of acylamino alkane sulfonates.

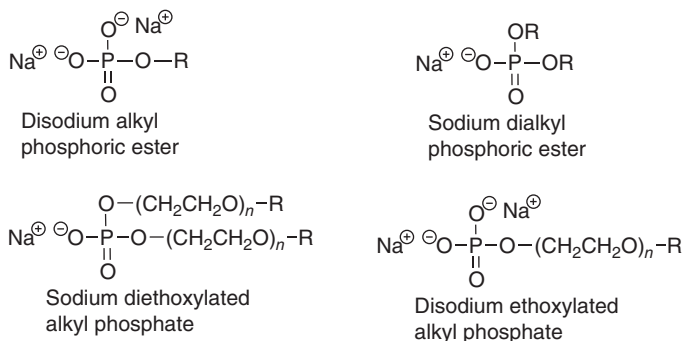


Figure 10.30 Chemical structure of alkyl phosphates and alkyl ether phosphates.

10.4.3 Phosphoric Acid Esters and Salts

This class of surfactants includes alkyl phosphates and alkyl ether phosphates (see Figure 10.30). Phosphate esters are used in formulations where a particular tolerance to pH, heat, or electrolytes is required. They are also used in acidic cleaning products for household as well as industrial applications. They act as metal stripping or dipping agents, which increase paint adhesion. The phosphate esters also show antistatic properties to the treated substrates. Incorporated in dry-cleaning compositions, phosphate esters provide an exceptional detergency. The less water-soluble phosphate esters are also used as antifoaming agents and are applied as emulsifiers in agrochemical applications.⁵

10.4.4 Acylamino Acids and Salts

Acyl amino acids and salts, which are anionic surfactants, can be classified into the following three categories:

Acyl glutamates: Acyl glutamates are based on α -aminoglutaric acid: $\text{HOOC}-\text{CH}_2-\text{CH}_2-\text{CH}(\text{NH}_2)-\text{COOH}$. These compounds (see Figure 10.31) are applied in PCPs such as shampoos, as they are mild to the skin and deliver improved skin feel.

Acyl peptides: Acyl peptides (see Figure 10.32) are formed from hydrolyzed proteins (e.g., animal collagen). The average polypeptide molecular weight can vary from about 350 to 2000. Acyl peptides are used in shampoos, are prone to microbial degradation, and are rather tolerant to water hardness.

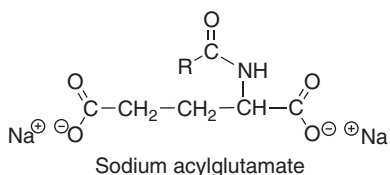


Figure 10.31 Chemical structure of sodium acylglutamates.

⁵ E.g., concentrated fertilizer solutions.

Figure 10.32 Chemical structure of sodium acyl polypeptide.

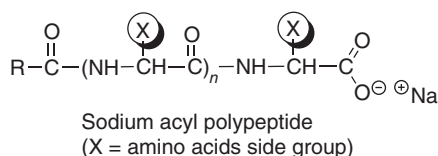
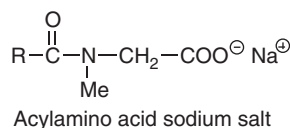


Figure 10.33 Chemical structure of salts of acylamino acids.



Acyl sarcosides: Sarcosinates (or salts of acyl amino acids) are the condensation products of fatty acids with *N*-methylglycine ($\text{CH}_3-\text{NH}-\text{CH}_2-\text{COOH}$) (or sarcosine) (see Figure 10.33). Sarcosinates are mild to the skin, and can be used as corrosion inhibitors.

10.5 Cationic Surfactants

A large group of this class of surfactants is composed of nitrogenated compounds such as amine quaternary ammonium salts, bearing one or several long chains as fatty amines (see Figure 10.34). These surfactants are in general more expensive for example than anionics, because of a high-pressure hydrogenation reaction that is required to be carried out.

10.5.1 Alkyl Amines

Primary, secondary, and tertiary alkyl amines and, especially, their salts are uncharged in neutral solution and therefore are not strictly cationic. They can be considered cationics in a pH low enough to provide the ionic form; otherwise, they must be considered as nonionics. Salts of fatty amines can offer germicidal activity; their fungicidal efficacy is enhanced when the amine is neutralized with salicylic or *o*-chlorobenzoic acid.

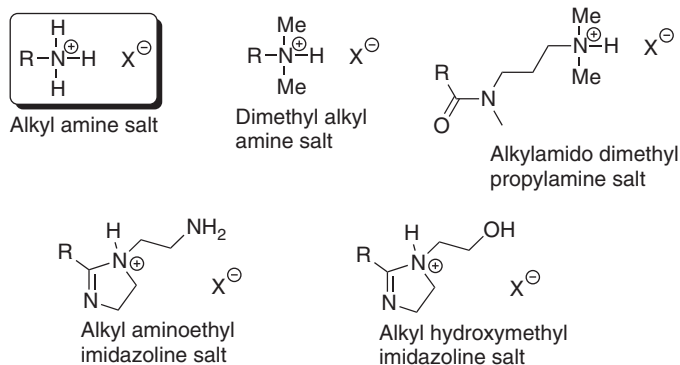


Figure 10.34 Structure of cationic surfactants (alkyl amine salts).

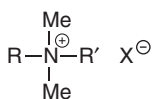


Figure 10.35 Structure of tetraalkyl(-aryl) ammonium salt.

Amines are used in textile treatment (e.g., antistatic treatment) and occasionally in rinse fabric softeners. Amido-amines are also used in cosmetic products. Salts of stearyl and tallow fatty amines are used in some mining applications (e.g., flotation process). Fatty amines, diamines and polyamines find other prospects as adhesive agents in the coating of damp surfaces with paint or bitumen and as corrosion inhibitors.

10.5.2 Alkylimidazolines

Imidazolines are cationic oil-in-water emulsifiers (see Figure 10.34). They adsorb to metal surfaces and improve the adhesion of the layer applied to substrates.

10.5.3 Quaternary Ammonium Compounds

10.5.3.1 Tetraalkyl(-aryl) Ammonium Salts

The water solubility of quaternaries depends primarily on the nature of R substituents⁶ (see Figure 10.35). Quaternaries carrying two or more long hydrophobic chains have very poor water solubility. Low-solubility quaternaries can adsorb to various substrates and impart various useful conditioning effects.⁷ Quaternaries are generally not compatible with anionics because of the formation of a water-insoluble complex.

The major use of quaternaries is related to their ability to adsorb to natural or synthetic substrates and fibers. They are less-soluble long hydrophobic chain containing compounds (e.g., C₁₆–C₁₈ dialkyldimethyl ammonium chlorides) deposited on fibers. Their softening and antistatic properties are similarly exploited in hair-conditioning shampoos or after-shampooing rinses. In cosmetic applications, quaternaries can cause ocular and local irritation; nevertheless, their potential for skin penetration is very low. Among the quaternaries, some are used as germicides, disinfectants, or sanitizers, being especially effective against gram-positive bacteria but less effective against gram-negative bacteria. Quaternaries are also used as emulsifiers in acidic creams and lotions. *N*-Alkyltrimethyl ammonium salts are used as emulsifiers in applications requiring selective adsorption of the emulsifier on the treated substrate.

10.5.3.2 Heterocyclic Ammonium Salts

Heterocyclic quaternaries are derived from heterocyclic aliphatic or aromatic compounds. They are often based on morpholine, imidazoline, pyridine, and isoquinoline (see Figure 10.36).

The quaternaries derived from imidazoline and morpholine are used as hair conditioners and antistatic agents. Those derived from aromatic heterocycles are

⁶ Hydrophobic chain lengths, polarity, etc.

⁷ Softening, antistatic, corrosion inhibition, etc.

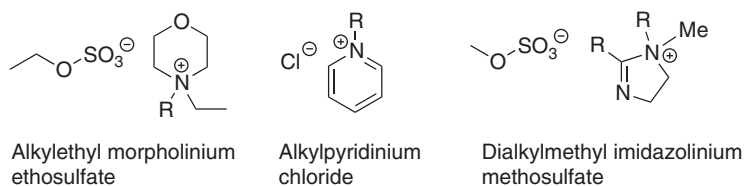


Figure 10.36 Structure of heterocyclic ammonium salts.

used as germicides. *N*-Alkyl imidazoline chlorides are also used as emulsifiers in applications where the adsorption of the emulsifying agent on the substrate is desired.

These surfactants can be considered as cationic or nonionic, depending on the degree of ethoxylation and on the pH at which they are used. Polyethoxylated amines are formed by ethoxylation of primary or secondary fatty amines. The poloxamines are formed by the reaction of ethylene diamine with propylene oxide. Other tetrafunctional products are obtained by successive reactions of ethylene diamine with ethylene oxide and propylene oxide. It must be noted that the above surfactants based on ethylene diamine, although intrinsically cationic, behave essentially as nonionic surfactants.

10.5.4 Ethoxylated Alkyl Amines

The ethoxylated alkyl amines are emulsifying agents in agrochemical emulsions, wax emulsions, and two-phase emulsion cleaners (see Figure 10.37). They are used as corrosion inhibitors in oil refineries. In personal care, ethoxylated alkyl amines act as emulsifiers and hair-conditioning agents.

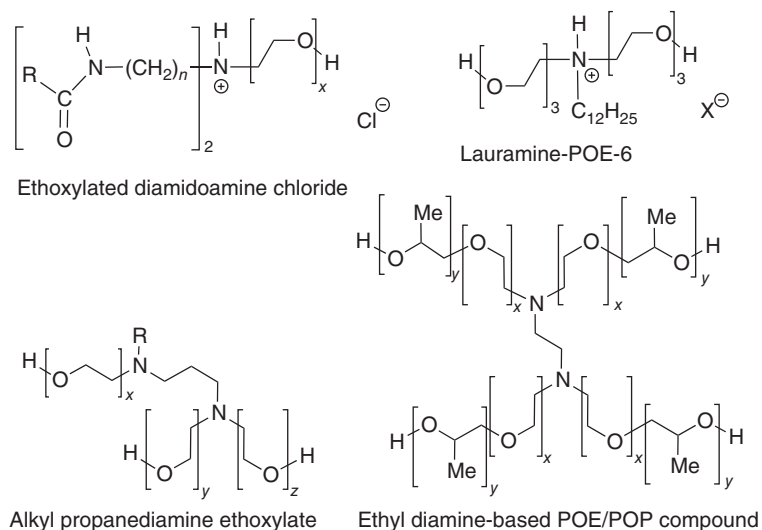


Figure 10.37 Structure of different ethoxylated alkyl amines.

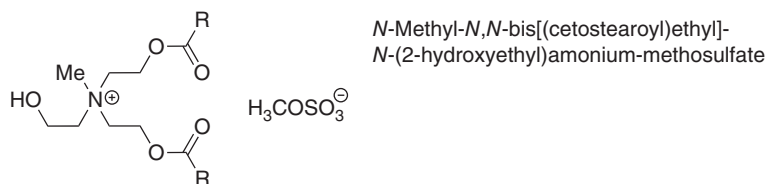


Figure 10.38 Structure of esterified quaternaries.

10.5.5 Esterified Quaternaries

Esterified quaternaries (or esterquats) show fabric-softening properties (see Figure 10.38). They are biodegradable and non-sensitizing agents, which could be used in dermatology. The esterquats are suitable substitutes for straight quaternaries with comparable softening properties.

10.6 Amphoteric Surfactants

Amphoteric surfactants, depending on the pH of the solution, show a positive or a negative charge. They exhibit a “zwitterionic” character, showing an isoelectric point.

10.6.1 Acyl Ethylenediamines and Derivatives

These surfactants show amphoteric properties and the zwitterionic form appears around neutral pH; the water solubility is minimal at the isoelectric point (see Figure 10.39).

Amphoterics of this class are similar to those of betaines. They are used in PCPs, baby shampoos, fabric softeners, and industrial and car cleaners. They are compatible with other surfactants and tolerate hard water and electrolytes.

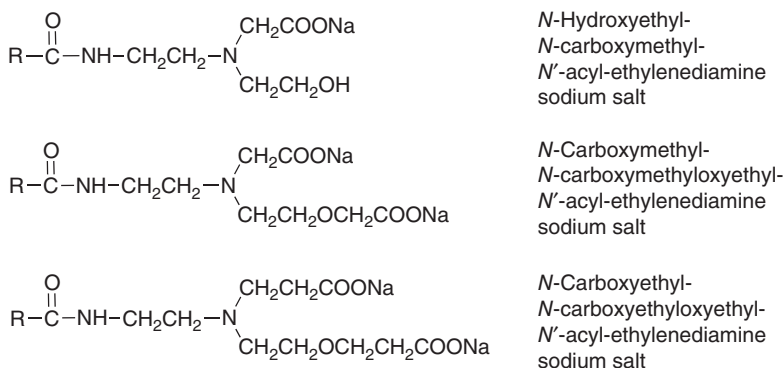


Figure 10.39 Structure of different acyl ethylenediamines.

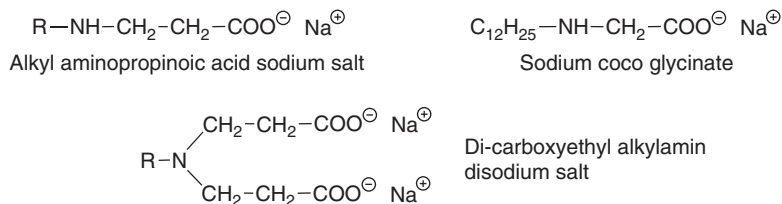


Figure 10.40 Structure of different *N*-alkyl amino acids.

10.6.2 *N*-Alkyl Amino Acids or Imino Diacids

These molecules are chemical derivatives of amino acids. *N*-Alkyl amino acids or diacid amphoterics are used in pcps and household products (see Figure 10.40). They are compatible with other surfactants, electrolytes, and hard water. They show good emulsifying, foaming, and wetting properties.

10.6.3 Alkyl Betaines

The positive charge is always carried by a quaternized nitrogen, whereas the anionic site can be a carboxylate (betaine), a sulfate, or a phosphate (see Figure 10.41). Betaines are good foaming, wetting, and emulsifying surfactants, especially in the presence of anionics. Detergency is best in alkaline conditions. Betaines are compatible with other surfactants and they frequently form mixed micelles; these mixtures often deliver unique properties that are not found in the individual constitutive surfactants. In their straight cationic form (i.e., in neutral and acidic conditions), betaines are not affected by water hardness ions or other metallic ions. They have hydrotropic properties, helping to solubilize

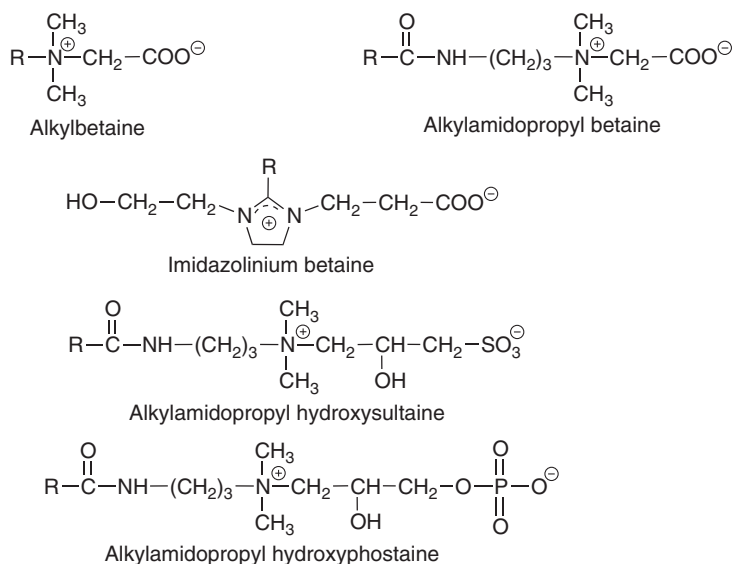


Figure 10.41 Structure of different alkyl betaines.

ethoxylated nonionic surfactants in the presence of salting-out ions. Betaines are especially mild to the skin and have the ability to improve skin tolerance against irritating anionic surfactants.

Betaines have various advantages in that they have low eye and skin irritation and their presence is known to decrease the irritation effect of anionics. However, due to their high price, they are usually used in combination with other surfactants. Betaines are thus especially suitable in personal-care applications (shampoos, foam baths, liquid soaps, shower gels, etc.), fabric hand-wash products, and dishwashing products.

10.7 Alkoxyated Polysiloxanes

Alkoxyated polysiloxanes are derived from polydimethyl siloxane, where methyl groups are substituted by hydrophilic groups that can be anionic, cationic, or nonionic. Silicone surfactants show excellent wetting capacity on low-energy surfaces (see Figure 10.42). Further, their diluted solutions can considerably weaken the surface tension to below 20 mN m^{-1} . Foam is easily controlled, and foaming efficacy is suppressed together with a decreasing ethylene oxide:propylene oxide ratio. Ethoxylated polydimethyl siloxanes are rather inert and exhibit excellent chemical stability.

These surfactants are used as additives in paints, foam-controlling agents, textile auxiliaries, wetting agents, and cosmetic preparations such as protective creams, body milks, shampoos, and conditioners. The adopted name for these surfactants in the cosmetic, toiletry, and fragrance industries is “dimethicone copolyol.”

10.8 Fluorosurfactants

Fluorosurfactants contain perfluoroalkyls chains $\text{F}^-(\text{CF}_2-\text{CF}_2)^-$, in which n ranges from 3 to 8 (see Figure 10.43). They are excellent wetting agents showing a critical surface tension of about 25 mN m^{-1} . Similarly to conventional

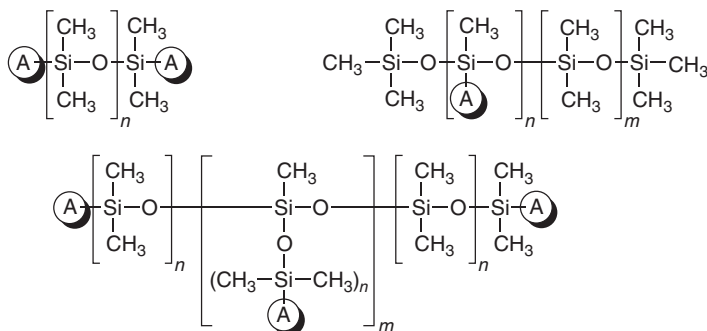


Figure 10.42 Structure of different polydimethyl siloxane. A denotes a hydrophilic group such as polyoxyethylene, amines, etc.

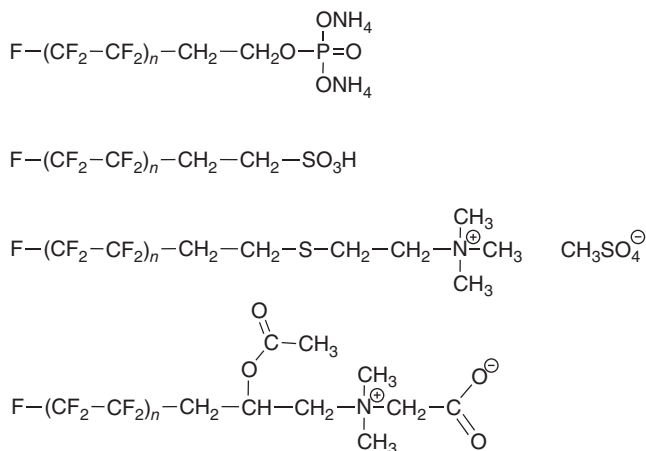


Figure 10.43 Examples of the structure of some fluorosurfactants.

surfactants, a rather broad variety of hydrophilic functions (ethoxylated chains, sulfonates, quaternaries, betaines, etc.) can be borne by fluorosurfactants. These hydrophilic groups are generally not directly grafted onto the fluorocarbon chain and are linked through a short intermediate hydrocarbon chain. Depending on their nature, these surfactants show variable emulsifying and foaming characteristics. They have excellent thermal and chemical stability. Therefore, they find prospects under those extreme conditions in which the hydrocarbon surfactants would decompose. The major drawback of fluorosurfactants is that they are not environment friendly because they resist to biodegradation. Murakami *et al.* [22] investigated the formation of perfluorinated surfactants from biodegradation of precursors.

Although they have some potential prospects in personal care (improved hair conditioning) and household products, fluorosurfactants find their major applications in industrial areas such as water-based adhesives, wetting agents, flotation processes, and battery technology.

10.9 Toxicological Aspects (Environmental Impact) of Surfactants

Most surfactants exert a remarkable environmental impact due to their surface activity, which can interact with the biological membranes of the aquatic organisms; therefore, they are more or less toxic. Often, the toxic effects of surfactants are related to the chain structure. Generally, a greater chain length in the 10–16 range, translates as stronger toxicity to aquatic organisms.

Most surfactants are not acutely toxic to organisms at environmental concentrations, as chronic aquatic toxicity of surfactants occurs at concentrations usually greater than 0.1 mg L^{-1} [20].

10.9.1 Environmental Impact of Alkylphenol Ethoxylates (APEOs)

APEOs have been used in industrial formulations (paper, leather, tannery, textile, oil, and metal-working industries), antifoamers, detergents, dispersants, emulsifiers, paint ingredients, pesticide adjuvants, and PCPs.

Biodegradation of APEOs was proven to be a significant source of 4-*t*-octylphenol (4-OP), and 4-NP environmental contamination [23]. These were extensively used until recently in the EU and in the United States as intermediates in the production of alkylphenol ethoxylates [24].

Potential effects include the following:

- Toxicity of 4-NP and 4-OP to algae, invertebrates, and fish at concentrations above the respective environmental quality standards of $1 \mu\text{g L}^{-1}$ (annual average) and $2.5 \mu\text{g L}^{-1}$ (maximum allowable concentration) for 4-NP and $1 \mu\text{g L}^{-1}$ (annual average) and $2.5 \mu\text{g L}^{-1}$ (maximum allowable concentration) for 4-OP in the water column.
- 4-NP has been found to have endocrine-disrupting effects in freshwater organisms at concentrations of $20 \mu\text{g L}^{-1}$ [25].
- The toxicity of NPEOs is well recognized, yet their replacements with less toxic linear alcohol ethoxylates has occurred only in the domestic sector.
- These compounds are considered as EDCs [26, 27], and when present at a certain concentration they may affect aquatic biota by mimicking or counteracting natural hormones,⁸ [28–30] being responsible for the adverse effects of this and related compounds on reproductive organs and developmental processes.
- In invertebrates, 4-NP reportedly interacts with developmental pathways of some crustaceans such as the elimination of testosterone [31], moulting [32], growth [33], and development of male secondary sex characteristics [34]. Due to the endocrine disruption properties of 4-NPs, morphological deformities of *Daphnia galeata* [35], mouthpart deformities in *C. riparius* [36], and the inhibition of barnacle settlement have been also observed [37].
- Alkylphenols have proved capable of inducing the production of vitellogenin in male fish at a concentration as low as $5 \mu\text{g L}^{-1}$ [20].

Articles concerning 4-NP and 4-OP exposure, human toxicity, and epidemiology in human population are limited. This highlights the urgent need to investigate the toxicity and biotransformation pathways of these compounds in the human body. Therefore, biomonitoring of 4-*t*-OP and 4-NP in human fluids and tissues is deemed necessary in order to help elucidate potential correlations between exposure and adverse health effects.

The use of APEOs has been restricted in many countries due to concerns about the environmental effects of the breakdown products of APEO, particularly 4-NP. Switzerland banned the use of NPEOs in domestic laundry detergents in 1986. Several countries in the EU also banned or restricted the use of NPEOs, 4-NP, and/or APEOs in the 1990s and early 2000s.⁹ Since 2000, 4-NP and 4-OP were included in the list of priority hazardous substances by Directive 2000/60/EC [38]. In the same year, Canada added 4-NP and NPEs to their Toxic Substances

⁸ Exhibits estrogenic activity and may disrupt the hormonal cycles of organisms.

⁹ E.g. since 1998 use of APEO in detergents has been forbidden in Germany.

List and required industrial users of these compounds to develop and implement Pollution Prevention Plans to reduce concentrations in the environment. Since January 2005, the EU Directive 2003/53/EC [10] has forbidden the use of NPEO in concentrations higher than 0.1% in formulations. These compounds will often end in the wastewater and consequently cause a problem in the environment. Currently, only a few countries (e.g., Asian countries) continue to use APEOs [23].

Scientific evidence on the toxicity of APEO degradation products prompted the inclusion of 4-NP and 4-OP in the EU list of priority hazardous substances in surface waters by Directive 2013/39/EC [39].

Nevertheless, 4-NP and 4-OP are still widespread and detected worldwide in environmental media, such as wastewaters, potable water, rivers, and biota [23, 40–42].

10.10 Environmental Occurrence of the Surfactants

After their use as household and industrial detergents, laundry products, and cleaners, surfactants and their metabolites are released into the environment in a myriad of products [20]. The relatively high levels reported are due in part to the exceptionally huge volumes of surfactants produced every year.¹⁰ [43]

Synthetic surfactants and their metabolites are discharged into aquatic ecosystems in treated or untreated wastewaters and enter various environmental compartments such as receiving waters and sediments at very high concentrations compared to other targeted analytes [44], despite removal efficiencies in WWTPs that are typically measured at between 95% and 99% [43]. However, according to other studies, these compounds are not effectively removed from WWTPs [45–47].

A range of anionic, cationic, amphoteric, and nonionic surfactants and antifoaming agents are commonly found in wastewater. Available studies on the presence, environmental behavior and distribution of these compounds are focused mainly on LAS [48–52] and NPEOs [50, 53–56].

Both the APEOs and their metabolites, alkyl phenols and carboxylic degradation products, have been shown to persist in the aquatic environment [57, 58]. Nonionic polyethylene glycol-based compounds are used as anti-foaming agents. Siloxanes are used in many PCPs such as anti-foaming agents and there is concern about their potential toxicity and transport in the aquatic environment [59]. Cationic surfactants include quaternary ammonium salts, such as cetrimonium chloride, and are used as emulsifiers, antiseptics, and homologs which have been identified as emerging contaminants in marine sediments [60]. Amphoteric surfactants include coconut-based products such as the widely used cocamidopropyl betaine. Anionic surfactants, including perfluorinated compounds such as PFOS and PFOA, have been used for over 50 years in food packaging and cookware coatings, paints and surfactants, cosmetics, and fire-fighting foams. They are found in wastewater and surface

¹⁰ Worldwide surfactant production is estimated to be above 10 million t.

water and are very persistent in the environment [61, 62]. PFOS was found in sewage effluent in Japan and has also been detected in surface water [63, 64].

Available data on the presence and distribution of aliphatic surfactants (AES and AEOs) are more limited compared to data on LAS and NPEOs, in spite of their production volumes being similar, although recent studies have reported AES [65–67] and AEO [68–72] levels at various sampling sites in Europe, Canada, and the United States.

Some surfactant classes (e.g., LAS, and NPEOs) possess chromophores and can be analyzed spectrometrically directly or by using ion-pair or post-column derivatization methods [43].

A study by the Barceló group [73] on the fate of APEOs and LAS in urban groundwater in the city of Barcelona (Spain) showed that levels of these compounds were higher in more urbanized areas. APEO degradation products prevailed in zones where the main recharge source was a river that receives large amounts of WWTP discharges. 4-NP diethoxycarboxylate (NP2EC), which was present at a maximum concentration of $11 \mu\text{g L}^{-1}$, was the most abundant APEO degradation product in the samples investigated. The 4-NP concentrations in groundwater were below $0.2 \mu\text{g L}^{-1}$ [73].

Corada-Fernández *et al.* [21] presented a study on the presence of the most commonly used surfactants, both anionic (LAS and alkyl ethoxysulfates, AES), and nonionic (alcohol polyethoxylates, AEOs, and NPEOs), in water and surface sediments from the middle stretch of the Guadalete river in southwest Spain. Average values were between 0.1 and 3.7 mg kg^{-1} in sediment, and between 0.2 and 37 mg L^{-1} in water. LAS concentrations were below 30 mg L^{-1} and the composition of their degradation intermediates (sulfophenyl carboxylic acids, SPCs) (160 mg L^{-1}) was dominated by short-chain homologs ($\text{C}_6 - \text{C}_9$ SPCs), indicating that the degradation of this surfactant is at an advanced stage.

10.10.1 Alkylphenol Ethoxylates (APEOs), and Their Degradation Products in the Environment

The common occurrence of APEOs in STP waters (particularly 4-NP and NPEO) is certainly due to their extensive domestic and industrial use. It was estimated that 60–65% of all alkylphenolic compounds that enter a conventional STP are discharged into the environment, and around 25% of these are alkylphenols [74]. WWTPs can remove 90–95% of primary compounds, but even if all 400 million pounds of 4-NP produced each year received 95% treatment, more than 10 million pounds of the chemicals would be released into the environment each year.

NPEO levels in the aqueous phase tend to be slightly lower than those for LAS as a consequence of the higher hydrophobicity and lower production volume of NPEOs. Their presence in surface waters and sediments has been attributed primarily to their incomplete removal in the sewage-treatment process [75, 76] and to the degradation products generated from the APEOs, such as alkylphenols and short-chain APEOs [77]. Concentrations of NPEO in surface waters have been reported worldwide:

- $<0.1\text{--}100 \text{ mg L}^{-1}$ in Mexico; [78], from 0.1 to 14.9 mg L^{-1} [53, 54, 79] in rivers in Holland, Switzerland, and the United States; and from 1 to 25 mg L^{-1} in

coastal waters of Israel [80], Italy [81, 82], Spain [68], and Denmark [83]. 4-NPs (and their metabolites) were present in over 61% of tested streams in a USGS study.

- APEO and 4-NP are found in water and suspended particulate material present in freshwater [68, 84–87], marine and estuarine environments [68], sediment [88, 89], wastewater [68, 84, 86, 87, 90–92], fish, and water [86, 92–94].
- 4-OP has been detected in surface waters at levels of 0.10 to 0.52 $\mu\text{g L}^{-1}$, and in wastewaters from 0.13 to 3.98 $\mu\text{g L}^{-1}$. The low levels of 4-OP detected in STP influents (1.26–3.98 $\mu\text{g L}^{-1}$) decreased further in the effluents. The influent concentrations (5.59–17.5 $\mu\text{g L}^{-1}$) were substantially reduced (by 75–97%) in the STP effluents [95].
- The fate of APEOs has been most extensively studied in Europe, where 4-NP concentrations in sludge have been extremely variable (0.02–2530 $\mu\text{g g}^{-1}$ dw [58]). Despite high removal efficiencies under some treatment conditions, APEs and their degradation products are commonly detected in WWTP effluents.
- Studies of wastewater effluents in Europe, Asia, and Canada have reported concentrations of 4-NP ranging from below detection to 343 $\mu\text{g L}^{-1}$, with most ranging from 0.2 to 2 $\mu\text{g L}^{-1}$ [58, 96]. In the United States, 4-NP concentrations in municipal effluents have generally ranged from 0.2 to 37 $\mu\text{g L}^{-1}$ [96–98].
- Degradation products of APEOs have been detected in groundwater from North America, Europe, and China [73, 99–103]. 4-NP ethoxylate degradation products were usually at higher concentrations than octylphenol ethoxylate degradation products. For instance, maximum concentrations of 4-NP and octylphenol in groundwater samples analyzed in a pan-European survey were 3.8 $\mu\text{g L}^{-1}$ and 41 ng L^{-1} , respectively [99].
- 4-NP was detected in the San Francisco estuary, in water (<2–73 ng L^{-1}), sediments (22–86 ng g^{-1} dw), and mussels (<0.04–95 ng g^{-1} ww), while 4-NP mono- and diethoxylates were detected in sediments (<1–40 ng g^{-1} dw) and mussels (<5–192 ng g^{-1} ww) [104]. Concentrations of 4-NP in soil could be expected to be higher than in water due to its physicochemical properties, that is, low water solubility (6.35 mg L^{-1}) and high hydrophobicity ($\log K_{\text{ow}}$ 5.71).
- Concentrations of surfactants in surface sediments can be higher than those measured in water: for example, from 0.1 to 50 mg kg^{-1} of NPEOs in Barcelona harbor [68] (Spain) and Jamaica Bay (NY) [105]. The 4-NPs concentration of the stock spiked sediment was between 6.0 and 6.6 mg 4-NP g^{-1} dw [106].

APEO and 4-NP have been found in human samples as follows:

- Calafat *et al.* [107] measured 4-OP in urine samples from a population of 2,517 children above the age of 6 yrs. 4-OP was detected in 57.4% of the participants with total (free plus conjugated species) concentrations ranging between 0.2 and 20.6 ng mL^{-1} .
- Tan and Mohd [108] measured 4-OP at 180 cord blood samples and 4-OP was detected in 31 samples in concentrations from <0.05 to 1.15 ng mL^{-1} . Bendtsen *et al.* [109] concluded that 4-OP exerts a sex-specific effect on male germ cells

by culturing human gonads (five testes and five ovaries). Ademollo *et al.* [110] studied the presence of 4-NPs, and 4-OPs in breast milk. 4-NP was found at the highest levels with mean concentrations of 32 ng mL^{-1} while 4-OP was found at a mean concentration of 0.08 ng mL^{-1} .

- Chen *et al.* [111] determined 4-NP and 4-OP in 59 human-milk samples and correlated findings with demographics and dietary factors. This study concluded that food patterns involving cooking oil and processed meat products are strongly associated with 4-OP concentration in human milk.
- Müller *et al.* [112] investigated levels of 4-NPs and 4-OP by analyzing human autopsy adipose tissue samples. 4-NP concentrations ranged from 19 to 85 ng g^{-1} lipids and 4-OP concentrations from 0.58 to 4.07 ng g^{-1} lipids. That study stressed that these values were both in the range of the analytical background contamination.
- Lopez-Espinosa *et al.* [113] also determined 4-NP and 4-OP concentrations in adipose tissue of 20 non-occupationally exposed women living in southern Spain. 4-NP and 4-OP were detected in 100% and 23.5% of the subjects, respectively. The median level of 4-NP was 57 ng g^{-1} and that of 4-OP was 4.5 ng g^{-1} of adipose tissue.
- Finally, Calafat *et al.* [114] measured only the isomer 4-*n*-nonylphenol in urine samples from a population of 394 adults, and 4-*n*-Nonylphenol was detected in 51% of the samples at a median concentration of $<0.1 \text{ ng mL}^{-1}$.

10.10.2 LASs and Their Degradation Products

A wide range of LAS concentrations in marine and fresh water [48, 49, 65, 68, 81, 115] have been reported: for example, from a few mg L^{-1} to several hundred mg L^{-1} in Tamagawa estuary [48] and Tega lake [78] (both sites in Japan), the Venice lagoon [116] (Italy), and the bays of Almeria [68], and Cadiz [51, 65] (both in Spain).

Notwithstanding their relatively high solubility, these compounds show a moderate to high sorption capacity, so that significant percentages are attached to suspended solids and finally become part of sediments. Concentrations of these surfactants in surface sediments can be higher than those measured in water, by several orders of magnitude, especially in polluted areas subjected to untreated wastewater discharges: for example, from 24 to 410 mg kg^{-1} of LAS in the Tamagawa estuary [48], the Tega lake [78] (Japan), and the Sancti Petri channel (Spain) [65].

10.11 Biodegradation of Surfactants

The massive worldwide use of surfactants requires them to be as innocuous as possible for the environment, that is, of low toxicity and high biodegradability. Biodegradation is a key factor for reduction and removal of organic contaminants from the environment. The evaluation of biodegradability of anthropogenic organic substances is an essential parameter for environmental risk assessment and required according to pertinent legislation [117].

Degradation of surfactants through microbial activity is the primary transformation occurring in the environment and an important process to treat surfactants in raw waste in STPs. During biodegradation, microorganisms can either utilize surfactants as substrates for energy and nutrients or co-metabolize surfactants by microbial metabolic reactions [20].

Biodegradation means the microbial degradation of organic substances. Depending on the degradation result, biodegradation with respect to surfactants is defined as follows [117]:

Primary biodegradation: means the structural change (transformation) of a surfactant by microorganisms resulting in the loss of its surface-active properties due to the degradation of the parent substance and consequent loss of the surface-active property.

Ultimate biodegradation: refers to the level of biodegradation achieved when the surfactant is totally used by microorganisms that break it down into inorganic end-products such as carbon dioxide, water, and mineral salts of any other elements present (mineralization) and new microbial cellular constituents (biomass).

Ready aerobic biodegradability: is an arbitrary classification of surfactants that have passed certain specified screening tests for final biodegradability.

The biodegradation process of organic compounds is affected by many factors, the most critical of which are the physiochemical characteristics of the compounds (solubility, concentration, structure, etc.), the physicochemical conditions of the environmental media (dissolved oxygen, temperature, pH, light, nutrient concentration, etc.) and the microorganisms present in the aquatic environment [18]. Most surfactants can be degraded by microbes in the environment, although some surfactants may be persistent under anerobic conditions [118]. Different types of surfactants have different degradation trends in the environment.

Biodegradation is influenced by several factors, including the number of microorganisms capable of metabolizing the organic compound, growth factors such as temperature, pH, nutrients, and water-content bioavailability of the organic substrate. For degradation of organic compounds at significant rates, an appropriate number of relevant microorganisms are needed. In biodegradation tests and technical biodegradation processes, the reaction can be initiated with an initial supply of microorganisms that are adapted to special conditions (e.g., aerobic or anerobic) and/or to the special compound used as substrate source.

Detergent surfactants can be found in wastewater in relevant concentrations. The natural environment is predominantly aerobic, which for a long time has led to a focus on the biodegradation results for chemicals under aerobic conditions, as required by European legislation. Thus, a number of international recognized standard test methods regarding the aerobic biodegradability of substances have been developed. Nevertheless, few environmental compartments lack free oxygen, such as river sediments and subsurface soil layers, as well as anerobic sludge digesters of WWTPs, which have strictly anerobic conditions.

Several systems for testing biodegradability are available [119]. Most of them have been developed for determining aerobic biodegradability of substances and

only a few for testing biodegradability under anerobic conditions. Some of the widely used biodegradation tests are the following:

Screening test: This is conducted according to the OECD 301 E test for ready biodegradability [120]. A solution of the surfactant, is inoculated and incubated under aerobic conditions in the dark at 25 °C for 21 d. The primary biodegradation is monitored by means of the residual-surfactant concentration over time using colorimetric methods in which the absorbance is directly proportional to the surfactant concentration. *Advantages:* Easy to prepare/carry out; Easy to analyze results. *Disadvantages:* Problems in the analysis of low surfactant concentrations; each inoculum differs; test time 21 days.

Confirmatory test: Performed according to the OECD 301 E test, this test is used for surfactants that have failed in the screening test either to confirm or reject the results. It consists of inoculating a small amount of microorganisms, from a secondary effluent-treatment plant that works preferably with domestic wastewater. Chemical oxygen demand (COD), and dissolved organic carbon (DOC) are measured daily to determine the biodegradation efficiency. *Advantages:* Easy to prepare/carry out; Easy to analyze results. *Disadvantages:* Bulking sludge causing solid loss by flotation; each sludge for each test being different; test time more than 1 month.

Respirometry test: This is applied using the system Oxitop Control[®],¹¹ which determines the manometric changes that occur when oxygen is consumed to transform the surfactant into CO₂ by the microorganisms inoculated (from an aerated, mixed population) in a mixture formed by the nutrient solution and the surfactant. *Advantages:* Easy to prepare and carry out automatic tracking.

***Pseudomonas putida* biodegradation test:** A monoculture strain *P. putida* CECT 324, is used in the biodegradation test. Erlenmeyer flasks are filled with the surfactant solution [121], the pH is adjusted to 7.0, and the flasks are inoculated with bacterial stock of *P. putida*. Flasks are incubated at 30°C, and at the beginning as well as after 72 h a sample of each flask is filtered and used to determine the dissolved organic carbon. Biodegradation efficiency is evaluated as a percentage. *Advantages:* Fast (72 h); *P. putida* being commonly present in activated sludge; reproducibility; use of a definite living system. *Disadvantages:* Problems in DOC measurements for low/high concentrations; possibility of contamination of the strain; requirement to work under sterile conditions.

Based on these considerations, the screening test and the respirometry test are the most reproducible and the easiest to perform, and they supply more information [18].

The reaction of the EDCs during wastewater treatment processes differs depending on the group of compounds involved. These in turn are determined by their physicochemical properties and the nature of the treatment process involved [96]. The biological degradability varies according to the nature of the

¹¹ WTW, Weilheim, Germany.

aliphatic chain. Generally, the linear chains are more readily degradable than branched chains.

Most surfactants can be degraded by microbes in the environment although some surfactants such as LAS and ditallow dimethyl ammonium chloride (DTD-MAC) as well as alkylphenols may be persistent under anerobic conditions. LAS were found to degrade in sludge-amended soils with half-lives of 7 to 33 d. Some polar pollutants in wastewaters are neither biodegradable nor can be biotransformed into persistent and toxic metabolites during their degradation [122]; they remain mainly as surfactants which are then discharged *via* wastewater.

The biodegradation of surfactants in WWTPs [123, 124] yields degradation products of LASs, which are long-chain sulfophenyl carboxylate compounds (SPCs) with more than five carbon atoms in the linear chain apart from the benzene ring. APEOs decompose by the progressive loss of ethoxylate groups to form short-chain APEOs (1–2 EO units) and alkylphenols (APs). NPEOs with more than eight EO units are readily degraded, usually with >92% efficiency [74].

10.11.1 Aerobic Biodegradation

In a recent study by Jurado *et al.* [18] on aerobic biodegradation of different surfactants, the following conclusions were drawn:

- Biodegradation results depend on the test used, the microorganisms used in the test, and the family of the surfactants tested.
- The surfactant structure influences biodegradability. Regarding the length of the alkyl chain, the effect depends on the family of surfactant: for the fatty alcohol ethoxylates and amine-oxide-based surfactants, the biodegradability is higher when the alkyl chain is longer, while, for the carboxylic derivative surfactants and alkyl polyglucosides, the opposite occurs.
- The initial surfactant concentration affects biodegradability. The greater the initial concentration, the lower the biodegradability, except for the amine oxides for which the effect is the opposite.
- The fatty alcohol ethoxylates, especially alkylpolyglucosides, can be considered to be the most biodegradable and the carboxylic derivative surfactants the least biodegradable, according to the mean biodegradation rate.

10.11.2 Anerobic Biodegradation

Anerobic biodegradation means the microbial degradation of organic compounds under conditions free of molecular oxygen. As opposed to aerobic biodegradation pathways, where organic compounds are often mineralized by one type of microorganisms the anerobic biodegradation of a substance up to the inorganic end-product stage always requires the presence of different types of microorganisms.

In the first step, complex or polymeric organic compounds are utilized by fermentative bacteria. Products of hydrolysis and acidification are metabolites of low molecular weight such as alcohols and short-chain fatty acids (C_2 – C_4 organic acids). Acetogenic bacteria subsequently utilize these fermentation products as substrates and transform them to acetate, carbon dioxide, and molecular hydrogen. At the end of the food chain, the methanogenic bacteria use acetic acid,

carbon dioxide, and hydrogen for the production of biogas (a mixture of methane and carbon dioxide).

Anerobic conditions in the environment occur when the oxygen consumption by biological oxidation processes exceeds the oxygen supply. This can happen either in small anerobic sectors in an otherwise aerobic system, or in large and stable compartments such as marine or freshwater sediments, moorlands, and poorly drained soils.

Biodegradation of LAS in the Guadalete river (Spain) has been studied by analysis of SPCs (LAS metabolites) in the aqueous phase. Sampling stations located upstream showed very high concentrations of short chain SPC homologs, indicating that the degradation of LAS by oxidation and progressive shortening of the alkyl chain has entered its final stage before mineralization. Downstream, however, the presence of sewage sources has increased the values of very reactive long chain SPC homologs and LAS concentrations, because the degradation process is just beginning to occur. Moreover, steric impediments can affect the progress of LAS degradation [21].

Most of the data on anerobic biodegradability have been found for anionic surfactants [125], and a summary of the results are listed in Table 10.2.

Aerobic conditions better facilitate the further biotransformation of APE metabolites than do anerobic conditions [96]. However, complete de-ethoxylation with the formation of APs has been observed only under anerobic conditions [133]. The primary degradation of APEs in a conventional STP or in the environment starts with the shortening of the EO chain, leading to

Table 10.2 Screening tests (anerobic biodegradability) of anionic surfactants.

Surfactant	Characterization	Test subst. (mg L ⁻¹) active matter	Test subst. (mg L ⁻¹) carbon	Inoculum (g L ⁻¹) dry matter	References
Soap	Na-palmitate, Na-laurate, Na-stereate	70–1,000		1–5	[126, 127]
LAS	C ₁₀ –C ₁₃	50		1–5	[128]
	C ₈ –C ₁₂		50		[129]
	C ₁₀ –C ₁₄		10–200	3–4.5	[130]
SAS	C ₁₄ –C ₁₇		20–100	3	[131]
AOS	C ₁₄ –C ₁₆		20–100	3	[131]
MES	C ₁₀ –C ₁₆		20–100	3	[131]
Dialkyl sulfo-succinates	di-C ₈ –SS		20–100	3	[131]
Monoalkyl ethoxy sulfo-succinates	C ₁₂ –(EO) ³ –SS		20–100	3	[131]
Sodium alkylether sulfate	C ₁₂		20	0.15	[132]
Alcohol ether sulfate	C ₁₂ –C ₁₄ 2 EO		50	1–5	[128]

short-chain APEs and APs [96]. The metabolites formed with only one (NP1EO) or two (NP2EO) ethoxy units and 4-NP are more persistent [134] and more toxic to aquatic organisms as endocrine disrupters than are the parent compounds (NPEnO) [122], being considered endocrine disrupters [77, 135].

In WWTPs, APEOs are biodegraded to form 4-NP, 4-OP, mono-, di-, and triethoxylates (e.g., NP1Es, NP2Es, NP3Es), and alkylphenoxy carboxylates (APECs). Most studies on the fate of APEOs in WWTPs have focused on NPEs and 4-NP, due to their extensive use, frequency of detection in WWTPs, and toxicity. Removal efficiencies depend on the WWTP location and type of treatment, and have been reported to vary between 50% and 99% for APEOs in general [136], 47 to 99% for NPEOs [20], and 9–94% for 4-NP specifically [58]. Degradation of APEs during wastewater treatment complicates the estimation of removal efficiency because the breakdown products may be present in higher concentrations in the effluents than in the influents [74, 98]. Most of the data on anaerobic biodegradability of nonionic surfactants are available for alcohol ethoxylates and glucosides [125].

Cationic surfactants are used in much lower amounts in detergent formulations compared to anionic and nonionic surfactants. According to the detergent regulation 684/2004, cationic surfactants should be ultimately biodegradable under aerobic conditions. Only a few data are available on the anaerobic biodegradability [125]. One problem encountered in biodegradation tests is the inhibition of cationics even at low concentrations [137]. Similar to cationics, the amphoteric surfactants are used in low amounts. Only a few data are available on anaerobic biodegradability [125].

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11

Personal-Care Products

11.1 Introduction

Personal-care products (PCPs) are of widespread use all over the world. Chemically speaking, PCPs are complex mixtures of chemicals in multiple forms such as creams, lotions, gels, solids, semisolids, stabilizers, emulsifiers, pH regulators, biocides, dyes, and many others. PCPs are used in soaps, shampoos, conditioners, toothpastes, skin care products, sunscreens, insect repellents, lotions, and fragrances. These consumer goods include many substances of special concern that can be considered as EPs. Chemicals that comprise PCPs also are numbered in the thousands. For example, in the world, enormous quantities of skin and dental care products, soaps, sunscreen agents, and hair styling products are used every year. Fragrances (e.g., nitro- and polycyclic-musks), UV blockers such as methylbenzylidene camphor, and preservatives such as parabens or isothiazolin derivatives, are frequently included in personal-care formulations, for chemical and biological stabilization.

One of the the most remarkable chemicals of such compounds are parabens, included not only in many PCPs but also in some household products, PCs, and food and beverage processing, because of their antioxidant and preservative properties. Other chemicals considered as EPs in PCPs are, for example, some active components of sunscreens such as camphor, methylbenzylidene or benzophenone, musks, such as components of fragrances and DEET as part of insects repellents. Finally, chlorophene and triclosan can be found in many antiseptics.

Unlike PCs, PCPs do not have to pass through the human body, because they enter the wastewater after their regular use during showering or bathing. This chapter focuses on the fate of such products, once they have been used by consumers and deposited in the environment.

11.2 Musks: Fragrances

Fragrances are synthetic or natural compounds that have a pleasant smell. They are present not only in perfumes but also in many other consumer goods. A

group of such compounds are musks,¹ which constitute a family of substances commonly used as base notes in perfumery because of their pleasant aromas and therefore are part of many personal-care or household products. Musks are often used in cosmetics and body-care products, such as perfumes and soaps, which contain “fragrance.” Musks are also used in air fresheners, detergents, fabric softeners, cleaning products, and cigarettes, and are also used as food additives.

With regard to the growing concern about musks, these products have been recognized as EPs by the scientific community, due to their persistence in the environment, and hazardous potential to ecosystems even at low concentrations, because they are widely present in environmental samples, including wildlife and humans. Musks are highly lipophilic, and therefore they tend to accumulate in sediment, sludge, and biota. Moreover, they can also accumulate in fat and this builds up in the human body. In fact, they have been detected in human breast milk, fat, and blood [1, 2].

Natural musks are glandular secretions from animals such as deer or muskrats but today most of these products used in the fragrance industry are of synthetic origin. Synthetic musks can be classified into the following groups:

- Nitro musks
- Polycyclic musks
- Macrocyclic musks
- Alicyclic musks

Figures 11.1 and 11.2 illustrate the different types of structures that make up the four groups of musks and the timeline when they were incorporated as artificial fragrances in consumer products.

Synthetic musk compounds are widely used as fragrance additives in many consumer products, including perfumes, lotions, sunscreens, deodorants, and laundry detergents. They can have nitroaromatic structures, such as musk xylene (MX), musk ketone (MK), musk ambrette (MA), musk tibetane (MT), or polycyclic structures, such as phantolide (AHMI), celestoid (ADBI), tonalide, and galaxolide (HHCB) (see Figure 11.1).

They are frequently found as key residues in WWTPs, both in the water and in the solid lines [3], and musks have also shown to be bioaccumulative substances and capable of being transported into the environment. Their widespread use has led to their presence in fish, and in rivers and lakes [4–10].

HHCB and tonalide are the most abundant musks in groundwaters from effluent and non-effluent-affected environments. Musk concentrations in non-effluent-impacted sites have been found to be lower than in effluent-impacted groundwater [11]. HHCB is the most investigated synthetic fragrance in groundwater [11–19]. In a nationwide study, in the United States, HHCB and tonalide were present in 11% and 16% of the groundwater samples investigated, respectively [14].

HHCB is also widespread in aquifers recharged with reclaimed water to prevent sea-water intrusion [17]. Overall, the musk concentrations in groundwater barely exceed 100 ng L⁻¹. However, HHCB concentrations up to 359 ng L⁻¹ and

1 See Glossary.

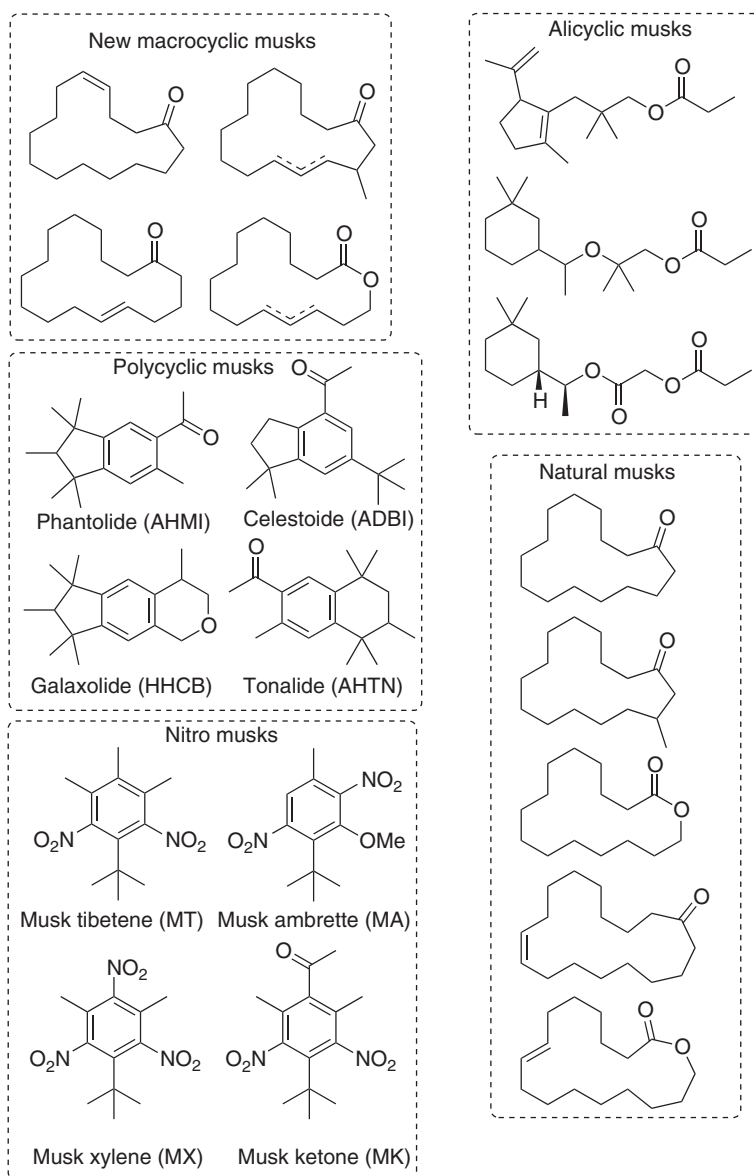


Figure 11.1 Main chemical structure of different types of musks.

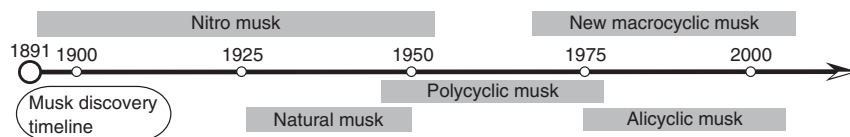


Figure 11.2 Timeline of the discovery of musks.

970 ng L⁻¹ were measured in groundwaters in Spain and in the United States, respectively [14, 17]. Extraordinarily high total concentrations of HHCb and tonalide (482 µg L⁻¹) were reported in the leachate from a landfill located on a sand/gravel pit [20]. Consequently, landfill leachates represent a relevant source of concern for these contaminants in groundwater.

Several new studies have been conducted for musks, including one by Chase *et al.* [11] who measured the environmental fate, transport, and transformation of six polycyclic musks and two nitro musks in wastewater, surface waters and their sediments, groundwater, soil cores, and plants from a treated wastewater land-application site.

HHCb and other musk compounds have been detected in fish from the Baltic and the North Seas, clearly showing its appearance in remote areas assumed to be emission points [21].

Musks can be absorbed through the skin and can be inhaled and ingested; skin absorption and inhalation are important routes of exposure through cosmetics. Up to 190 ng g⁻¹ lipid has been reported in humans [22]. The safety of musks with respect to human health has been extensively tested and affirmed by numerous regulatory agencies such as Scientific Committee on Cosmetic Products and Non-Food Products as well as academic scientists around the world; the presence of trace environmental levels of these compounds are continuously investigated, and environmental safety and monitoring studies are ongoing so that the public can be assured of the safety of these products [23]. Growing concerns about the health effects of nitro musks led the EU to ban the use of some of these chemicals in cosmetics and body-care products. Many companies have begun to replace nitro musks with polycyclic musks because the latter are believed to be less toxic [24].

Some musks irritate the skin or trigger allergic reactions [25–27]. Animal studies indicate that musks may disrupt the endocrine system [28–32], and may disturb a natural defense that the body uses to protect itself from toxic chemicals [33]. Laboratory studies also link some musks to cancer [34, 35], and others to nervous-system damage [36–38].

11.3 Biocides

Biocides are a variety of substances that are used to control organisms harmful to human or animal health, or that cause damage to human activities. Under this classification are included pesticides, wood preservatives, plastics, fibres, anti-fouling paints for the protection of ship hulls, and disinfectants and antiseptics in the manufacture of many commercial goods.

In 2005, the Non-Prescription Drug Advisory Committee of the USFDA was convened to discuss the potential benefits and risks associated with antiseptic products marketed for consumer use, such as soaps labeled as “antibacterial.” The conclusion of the FDA meeting resulted in a call for further research regarding the risks and benefits of specific consumer antiseptic products used in the community setting [39].

ABs are critical to treat bacterial infections (see Chapter 5). However, after years of overuse and misuse of these drugs, bacteria have developed antibiotic resistance, which has become a global health crisis [40, 41]. The relatively recent increase of surface antibacterial agents or biocides in healthy households may contribute to the resistance problem. The antibacterial substances added to diverse household cleaning products are similar to antibiotics in many ways. When used correctly, they inhibit bacterial growth [42].

Surface antibacterial substances were developed to prevent the transmission of disease-causing microorganisms among hospital patients. Tuberculosis, food poisoning, cholera, pneumonia, strep throat, and meningitis are just a few of the serious diseases caused by bacteria. Hygiene is one of the best ways to curb the spread of bacterial infections. Traditionally, people washed bacteria from their bodies and homes using soap and hot water, alcohol, chlorine bleach, or hydrogen peroxide. These substances act nonspecifically, meaning they wipe out almost every type of microbe (fungi, bacteria, and some viruses) rather than singling out a particular variety.

During the beginning of the 1990s, only a few dozen products containing antibacterial agents were being marketed for household use. Lately, however, consumers are getting the message that washing with regular soap is insufficient. The public is being bombarded with advertisements for cleansers, soaps, toothbrushes, dishwashing detergents, and hand lotions, all of which contain antibacterial agents. Body soaps, household cleaners, sponges, even mattresses and lip glosses are now packing bacteria-killing ingredients, and scientists question what place, if any, these chemicals have in the daily routines of healthy people.

For more than 700 household products containing antibacterial agents, no added health benefit has been demonstrated [42]. Similar to ABs, these products can select for resistant strains and, therefore, overuse in the home can be expected to propagate resistant microbial variants [43–45].

When a bacterial population is placed under an antibacterial chemical, a small subpopulation armed with special defense mechanisms can develop. This cross-resistance has already been demonstrated in several laboratory studies using triclosan, one of the most common chemicals found in antibacterial hand cleaners, dishwashing liquids, and other wash products. There is increasing concern on the use of household cleaning and hygiene products labeled as antibacterial as a result of laboratory data showing a link between exposure to ingredients in these products, particularly triclosan, and emergence of antimicrobial drug resistance [46].

11.3.1 Triclosan

Triclosan is an antibacterial and antifungal agent used as a biocide in personal hygiene products since the 1960s, and now is the most prevalent biocide ingredient in consumer liquid hand soaps (see Figure 11.3) [47]. It was first introduced in the health-care industry as a 1% component of surgical scrub in 1972 and for oral care in toothpaste in Europe in 1985 [48]. Although the FDA does not formally

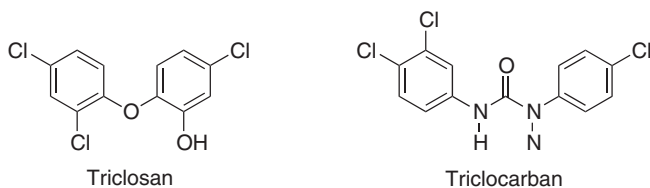


Figure 11.3 Structure of triclosan and triclocarban.

regulate the levels of triclosan used in consumer products, most of the popular liquid hand soap brands contain between 0.1% and 0.45% wv.

A chemically related compound, triclocarban, is used in antibacterial bar soap formulations. Triclosan is a nonionic, off-white, odorless, and tasteless powder, originally developed by Ciba-Geigy company, in the early 1960s [49]. Triclosan exhibits excellent chemical stability and formulary compatibility. The USFDA recognizes triclosan as an over-the-counter or prescription drug based on formulation and application. In addition, the FDA recently approved a New Drug Application for the use of triclosan for an over-the-counter oral-care product (toothpaste) at similar concentration levels as found in topical products. The drug has been recently reviewed and qualified for listing as a U.S. Pharmacopeia ingredient. Triclosan has also been accepted by the USEPA under the Federal Insecticide, Fungicide, and Rodenticide Act for use as an antimicrobial pesticide for fungicide/fungistat and bacteriostat applications [48].

Triclosan also exhibits some antiviral and antifungal activity [49]. It is bacteriostatic at low concentrations and bactericidal at high concentrations [50], inhibiting the growth of both gram-positive and gram-negative bacteria *in situ*, with varying effectiveness across bacterial species [49]. Although its bactericidal activity involves some nonspecific killing mechanisms, the bacteriostatic action occurs by inhibiting a specific bacterial target (enoyl-acyl carrier protein reductase) [51]. Similar to systemic antibiotics, triclosan has a mechanism for killing bacteria and when bacteria are exposed to triclosan *in vitro*, can confer resistance to antibiotics [52–54]. Triclosan shares this bacterial biosynthetic fatty acid pathway target with the antibiotic isoniazid [51].

Triclosan is also used in textile fibers and plastics against deterioration due to microbes, and consequently, it is widespread in the environment [55]. This product is marketed under the trade name Microban® when used in plastics and clothing, and Biofresh® when used in acrylic fibers. Triclosan has been extensively studied in human and animal investigations over a broad concentration range in numerous formulations. As an active ingredient, its safety has been established through acute toxicity, chronic toxicity, mutagenicity, reproduction, and teratology [49, 56, 57]. Several studies demonstrated laboratory evidence of triclosan-adapted cross-resistance with antibiotics among multiple species of bacteria [39].

Most of the studies on the occurrence of PCPs in groundwater include triclosan as target compound. In a European groundwater survey, this compound was found in only 2% of the samples analyzed, and at a maximum concentration of 9 ng L⁻¹ [58]. However, values of triclosan as high as 2110 ng L⁻¹ were measured

in the United Kingdom in a different study [59]. Overall, it is a widespread groundwater contaminant, reaching concentrations ranging from 1 ng L^{-1} to 345 ng L^{-1} in groundwater used as drinking water in Mexico [60]. Concentrations below 53 ng L^{-1} were detected in groundwater affected by reclaimed irrigation water [61], and slightly lower concentrations (11 ng L^{-1}) were even measured in groundwater not affected by wastewater in northern China [62]. This compound and an additional antiseptic agent, methoxy-triclosan, were also detected in cave stream systems in the United States [63]. After a single application of biosolids contaminated with $10.0 \mu\text{g g}^{-1}$ of triclosan and $4.9 \mu\text{g g}^{-1}$ of triclocarban, low concentrations of these antimicrobials were detected 2 m below the soil surface [64]. However, triclosan and triclocarban were also reported to be below the method limit of detection in other different monitoring studies [62, 65].

Both triclosan and its close chemical relative triclocarban (also widely used as an antibacterial), are present in 60% of streams and rivers in the United States. Both chemicals are efficiently removed from wastewater in treatment plants but end up becoming sequestered in the municipal sludge, which is used as a fertilizer for crops, thereby opening a potential pathway for contamination of food [66].

Triclosan has also been found in human breast milk, although not in concentrations considered dangerous to babies, as well as in human blood plasma. There is no evidence showing that current concentrations of triclosan in the human body are harmful, but recent studies suggest that it acts as an endocrine disrupter in bullfrogs and rats [66].

There are still no data available on the occurrence of the main biological TP of triclosan, methyl-triclosan, in groundwater. Methylated derivatives are less water soluble than parent compounds [67]. Consequently, methyl-triclosan concentrations in groundwater are not expected to be very high. Additional TPs of triclosan are chlorophenols and chlorophenol derivatives [55]. One of the main TPs generated during triclosan photolysis is 2,4-dichlorophenol (2,4-DCP). This compound was detected at concentrations below 340 ng L^{-1} in 10% of the groundwater sampled in a Danish national monitoring survey [68].

11.3.2 Chlorophene and Dichlorophene

Dichlorophene is a halogenated phenolic compound that functions as a bactericide and fungicide in cosmetics (see Figure 11.4). Chlorophene is a halogenated phenolic compound used as a biocide and preservative in cosmetics (see Figure 11.4).

Dichlorophene is a white or light-tan powder, while chlorophene occurs as white or off-white crystals. In cosmetics and PCPs, dichlorophene and chlorophene are used in the formulation of hair tonics, dressings, and other

Figure 11.4 Structure of chlorophene and dichlorophene.



hair grooming aids, as well as foot powders and sprays. Dichlorophene and chlorophene help to cleanse the skin or to prevent odor by destroying or inhibiting the growth of microorganisms. Chlorophene also prevents or retards bacterial growth, and thus protects cosmetics and PCPs from spoilage.

The FDA includes dichlorophene on its list of indirect food additives. It is permitted for use as a component of adhesives having incidental contact with food. The safety of dichlorophene and chlorophene has been assessed by the Cosmetic Ingredient Review Expert Panel.

Dichlorophene was reported to be used in cosmetic formulations at concentrations of 0.5% to 1.0%, but chlorophene was not reported to be used. Dichlorophene is prohibited for use in cosmetic ingredients in Japan. In Europe, the maximum authorized concentration allowed for dichlorophene is 0.5% and for chlorophene it is 0.2%. The major impurity of dichlorophene is the trimer 4-chloro-2,6-bis(5-chloro-2-hydroxybenzyl) phenol [69].

In rats, sulfate and glucuronide conjugates were the major metabolites of both dichlorophene and chlorophene. These metabolites were excreted in the urine. Chlorophene was incompletely absorbed through the skin. These chemicals exhibited low toxicity in acute oral-toxicity studies. Some evidence of toxicity with both chemicals was found in short-term oral-toxicity studies; kidney effects were the principal findings [69].

Chemicals that are toxic to the endocrine system are known as “endocrine-disrupting chemicals” (see Chapter 4) and dichlorophene is one of them. Dichlorophene is especially toxic to the endocrine system because it mimics estrogen [70]. This can lead to critical hormone imbalances in both men and women that can completely upset the body [69].

Dichlorophene is commonly used as a pesticide because it is toxic to many organisms, including bacteria and fungus, and it is also toxic to humans, by irritating the skin, being injurious to the eyes and mucus membranes, and being harmful when eaten or inhaled [69, 71]. Dichlorophene is positive in the Ames mutagenicity test, meaning that it has the potential to cause cancer. Despite this, dichlorophene has been added to cosmetics to kill bacteria and fungus [69].

Dichlorophene enters the environment through channels that cannot be individually controlled. Lange *et al.* [72] have identified the antimicrobials triclosan, chlorophene, and dichlorophene, ingredients in a variety of household and PCPs, as among the antiandrogens present in wastewater effluents that bioconcentrate in fish bile at concentrations tens of thousands greater than in the effluent itself [73]. Due to their occurrence in wastewater effluents and their ability to bioconcentrate, these compounds are considered to be bioavailable to fish. The antimicrobials are present in effluents at ng to low $\mu\text{g L}^{-1}$ concentrations and for resin acids from low ng up to mg L^{-1} concentrations. All these compounds have been shown to exhibit similar to higher antiandrogenic strengths *in vitro* on humans when compared with the standard antiandrogenic compound flutamide [73].

11.3.3 Parabens

The so-called parabens are a group of *p*-hydroxybenzoic acid ester derivatives (methyl, ethyl, propyl, isopropyl butyl, isobutyl, or benzyl) (see Figure 11.5).

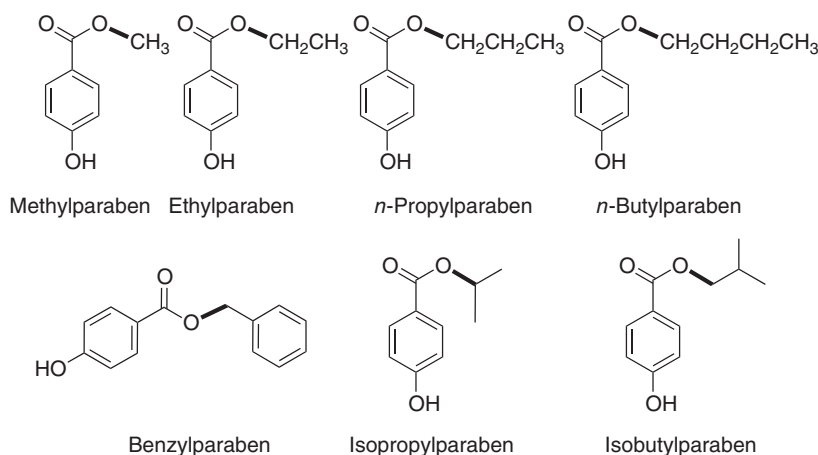


Figure 11.5 Chemical structure of seven alkyl esters of *p*-hydroxybenzoic acid (parabens), with the ester O – C bond in bold.

This family of compounds has been used as efficient antimicrobials since the mid 1920s. They are used in the manufacture of many daily-life products because of their fungicidal and bactericidal properties to preserve, such as in household products, cosmetics, PCs, and food and beverage. Some plants such as blueberries, carrots, olives, strawberries, and others produce parabens (mainly methylparaben) for their presumed antimicrobial activity [74].

Parabens are synthesized by conventional esterification reaction of *p*-hydroxybenzoic acid with the corresponding alcohol in the presence of an acid catalyst (e.g., H_2SO_4 or *p*-toluenesulfonic acid). Parabens are stable in acidic solutions [75].

Parabens are commonly used in cosmetics due to their antibacterial activity and their stability at different temperatures and pH levels. In addition, parabens do not alter or react with the active ingredients in products because parabens are fairly inert. However, the real driving force behind the widespread use of parabens is that they are extremely inexpensive. In 1996, the first evidences of the occurrence of parabens in water arose when some analytical data were published. Although these compounds are biodegradable, they are ubiquitous in surface water and sediments, due to their continuous release into recreational waters and domestic, urban, and industrial wastewaters, random discharge (direct discharge of non-treated sewage water), or leakage of municipal wastewater mains. Methyl-, ethyl-, propyl- and butylparaben are used in cosmetics, though methyl- and propyl-paraben are the most commonly detected. Parabens and chlorinated derivatives are frequently found at the low ng L^{-1} level in the aquatic compartment, and therefore they may be considered as emerging contaminants [76].

Laboratory studies suggest that parabens can disrupt reproductive hormones [31, 77–85]. Parabens are estrogenic molecules but exert weaker activity than natural estrogens, which would imply a low risk. In addition to use of paraben-containing products, humans may be secondarily exposed to parabens and their metabolites through the environment [55]. In 2006, the Centers

for Disease Control tested urine samples from a group of 100 adults and found detectable levels of methyl- and propylparaben (43.9 and 9.05 ng mL⁻¹, respectively) in nearly all the samples [86]. Furthermore, humans can be also exposed to parabens through their diet, which could be another critical source of environmental paraben exposure [87].

Parabens and their metabolites are known to be efficiently excreted through the urine [88]. Ecological-risk assessments for seven individual parabens have suggested that these compounds only pose a low risk in the environment, despite the effects on the reproductive systems already observed in fish [89].

Biodegradation takes place because the ester bond is easily broken (see Figure 11.5), to give the corresponding alcohol and the starting product *p*-hydroxybenzoic acid. An added problem is that parabens and their degradation products are capable of being chlorinated in water-disinfection processes by reaction of free chlorine with phenolic moieties, yielding halogenated by-products (see Chapter 12). These chlorinated phenolic by-products are even more stable and persistent than the parent species and they have been detected in wastewater, swimming pools, and rivers [76]. Despite efficient removal with conventional sewage treatments, parabens have still been detected in river-water samples at low concentrations in the ng L⁻¹ range [76]. Data concerning the presence of parabens in surface waters are shown in Table 11.1 [90].

In general, the highest frequency of detection and concentration values were recorded for the species most commonly used in cosmetics: methyl- and/or propylparaben. Their concentrations in Chinese rivers reached the levels of

Table 11.1 Concentration ranges (ng L⁻¹) of parabens detected in surface water.

Country	Methyl-paraben	Ethyl-paraben	Propyl-paraben	Butyl-paraben	[Ref.]
Southern China (Pearl river delta)	n.d.–1062	–	n.d.–3142	n.d.	[91]
UK (South Wales)	<0.3–400	<0.5–15	<0.2–24	<0.3–52	[92]
Spain (Galicia)	1.8–17.3	n.d.–3.0	n.d.–69	n.d.–7.0	[93]
Switzerland (North-eastern)	3.1–17	<0.3–1.6	<0.5–5.8	<0.2–2.8	[94]
India (Southern)	n.d.–22.8	2.47–147	n.d.–57.0	n.d.	[95]
Japan (Tokushima and Osaka)	25–676	<1.3–64	<0.8–207	<0.6–163	[89]
Japan (Central Pacific)	2.1–5.4	n.d.	4.9–25	n.d.–12	[96]
U.S. (Pittsburgh)	2.2–17.3	n.d.	n.d.–12	n.d.–0.2	[97]
Portugal (Ria de Aveiro)	<1.6–62	<0.3–6.7	<0.5–64	<0.2–42	[98]

1062 ng L⁻¹ and 3142 ng L⁻¹, respectively [91]. The maximum concentrations detected in European rivers were lower, reaching a maximum of 400 ng L⁻¹ for methylparaben [92] and 69 ng L⁻¹ for propylparaben [93]. (e.g., the total paraben levels in rivers were measured at 0.085 µL⁻¹ in Belgium [99].) Measured concentrations of ethylparaben and butylparaben in water samples were up to 147 ng L⁻¹ (ethylparaben) [95] and 163 ng L⁻¹ (butylparaben) [89]. Benzylparaben was rarely detected in water samples, with very low concentrations reaching maximally 4.4 ng L⁻¹ [94]. Although there are limited data on the occurrence of these types of compounds in groundwater, methylparaben and propylparaben have commonly been detected in groundwater in the United Kingdom [100]. Moreover, due to their physicochemical properties, they are expected to partition into the water phase, because parabens with short alkyl chains are more water soluble (0.5–20 g L⁻¹) and less hydrophobic (log K_{ow} in the 1.66–3.56 range) [90]. In terms of abundance, concentrations up to 5000 ng L⁻¹ and 5500 ng L⁻¹ were measured for methylparaben and propylparaben, respectively [59]. Methyl- and propylparaben were detected at up to 2.4 µL⁻¹ in municipal wastewater in Canada [101] and up to 3 µL⁻¹ in raw sewage water from a wastewater-treatment facility in Spain [102].

The results concerning paraben presence in drinking water are contradictory. Ferreira *et al.* [103] reported occurrence of methylparaben in tap water at concentrations of around 15 ng L⁻¹ (17 ± 4 ng L⁻¹), while Loraine and Pettigrove [104] did not detect MePB in treated drinking water.

Among the investigated parabens of three untreated leachates, methyl-, propyl-, and butylparabens were detected with median and maximum concentrations of 3480–7930, 900–1820, and 420–470 ng L⁻¹, respectively [105]. Nuñez *et al.* [106] analyzed series of parabens in forestry and agricultural soils and sediments from different areas of Spain. The values recorded were up to 6.35, 5.10, 0.29, 4.03, 0.45, 0.71 ng g⁻¹ dw for methyl-, ethyl-, isopropyl-, propyl-, benzyl- and butylparabens, respectively. The highest concentrations in sediments, have been observed for methylparaben (476 ng g⁻¹) [107], ethylparaben (60 ng g⁻¹) [107], propylparaben (64.5 ng g⁻¹) [108], and butylparaben (34 ng g⁻¹) [108]. Parabens have been detected in soil from agricultural soils, possibly from irrigation or fertilization practices [109]. Soil concentrations ranged from 0.5 to 8 ng g⁻¹.

The dust in houses has also been found to contain parabens [110]. Parabens present in indoor dust and air presumably originate from PCPs used in households (house dust contained up to 2400 ng g⁻¹) [111, 112].

Not surprisingly, current regulations on paraben use differ from country to country. In 2009, the Danish Environmental Protection Agency published a comprehensive report strongly emphasizing that parabens in lotions and sunscreens (especially propyl- and butylparaben) should be considered as a possible risk in young children due to potential endocrine-disrupting effects, which might manifest in adult life [113].

Parabens are therefore not included in the EU Annex1 list of dangerous substances of EU Council Directive 67/548/EEC. The highest allowed concentration of parabens in cosmetics is 0.4% for any individual paraben and 0.8% for paraben mixtures as defined in the EU Cosmetic Directive in 2000 [113]. While FDA limits

the levels of parabens allowed in foods and beverages, it does not regulate these chemicals in cosmetics or body-care products.

11.4 Sunscreen Agents: UV Filters

UV filters are being used increasingly due to growing concern about UV radiation and skin cancer, especially as a result of ozone depletion [114]. UV filters are common ingredients in many cosmetics and PCP, such as sunscreens, soaps, shampoos, and hair sprays [115–117]. Increasing interest has been shown in UV filters due to their presence in environmental waters and their potential for endocrine disruption and developmental toxicity. A few UV filters have estrogenic effects similar to E2 (a natural estrogen) as well as the potential for developmental toxicity [118].

There are two types of UV filters, organic UV filters, which work by absorbing UV light, and inorganic UV filters (e.g., TiO_2 , ZnO), which work by reflecting and scattering UV light. Organic UV filters are increasingly used in PCPs, such as sunscreens, cosmetics, beauty creams, skin lotions, lipsticks, hair sprays, hair dyes, and shampoos. Examples include benzophenone derivatives, oxybenzone (benzophenone-3), 3-benzylidene-camphor and 4-methylbenzylidene camphor (4-MBC); homosalate (3,3,5-trimethylcyclohexyl 2-hydroxybenzoate, HMS); ethylhexyl methoxycinnamate (EHMC); iso-amylmethoxycinnamate (IAMC); octyl-methoxycinnamate (OMC); derivatives of 4-aminobenzoic acid (PABA) known as padimates (ethylhexyl-dimethyl-PABA, octyl-dimethyl-PABA, isoamyl-dimethyl PABA); octocrylene (OC); and phenylbenzimidazole sulfonic acid (PBSA) (see Figures 11.6 and 11.7).

The majority of these are lipophilic compounds (low water solubility) with conjugated aromatic systems that absorb UV light in the wavelength range of 280–315 nm (UVB) and/or 315–400 nm (UVA) (see Figure 11.8). Most sunscreen products contain several UV filters, often in combination with inorganic micropigments [118]. UV filters or zinc oxide were present in 22.5% of 4447 products of all 5667 cosmetic products examined by the Chemical and

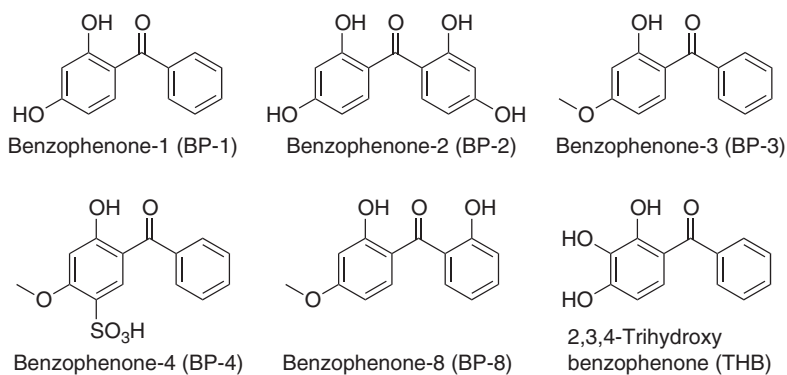


Figure 11.6 Chemical structure of benzophenone-3 and derivatives.

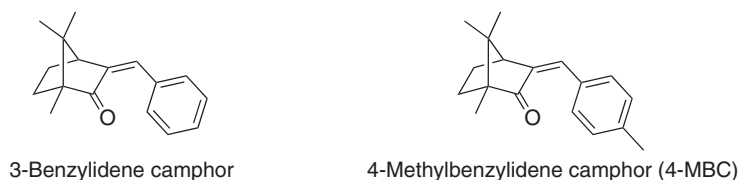


Figure 11.7 Structure of main benzylidene camphor derivatives.

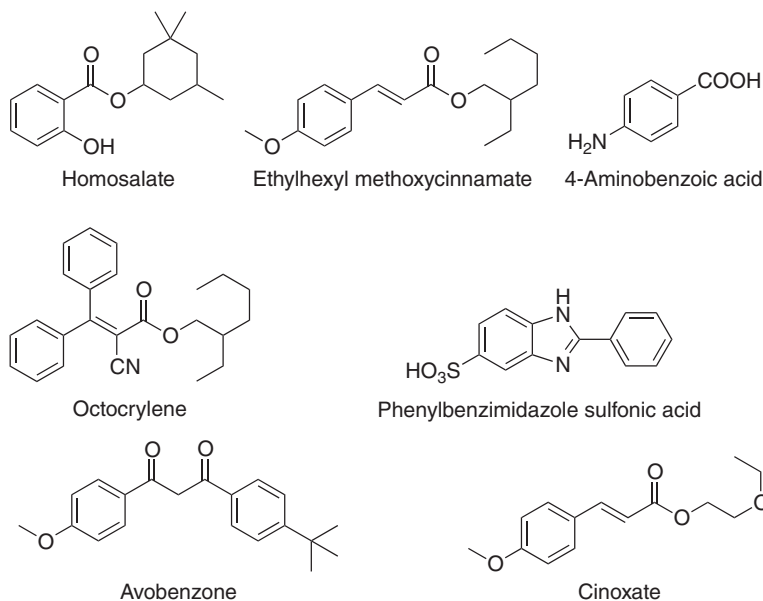


Figure 11.8 Structure of main UV filters.

Veterinary Investigation Office in Karlsruhe in a study performed in 2006–2009. Frequently, several different UV filters were included in one product. The most frequent UV filters were butyl methoxydibenzoylmethane and titanium dioxide, combined mostly with octocrylene in sunscreens and with ethylhexyl methoxycinnamate in creams [119].

The contents of 18 permitted chemical UV filters in 75 sunscreen products were determined by Rastogi [120]. The maximum content (29.3%) of chemical UV filters was found in a product that contained six UV filters. Octyl methoxycinnamate (1.4–4.7%) and butyl methoxydibenzoylmethane (0.4–4.8%) were the most frequently used UV filters, present in 49% and 44%, respectively, of the investigated products. UV filters are added to consumer sunscreen products at different concentrations due to sunscreen formulations [115, 117, 121–123]. The levels of UV-filters in sunscreens vary from 0.5 to 10%, sometimes reaching 25% [124].

11.4.1 Analysis of UV-Filters

Cuderman and Heath [125] described a procedure for isolating and determining UV-filters (homosalate, 4-methylbenzylidenecamphor, benzophenone-3,

octocrylene, butylmethoxydibenzoylmethane, ethylhexyl methoxycinnamate). Water samples were filtered, acidified, and extracted by use of solid-phase extraction. Extracted compounds were then derivatized before analysis by GC/MS. These methods indicated the detection limits of 13–266 ng L⁻¹ for UV-filters. The most abundant UV-filter was benzophenone-3 (11–400 ng L⁻¹). Bratkovics and Sapozhnikova [126] reported a new LC-MS/MS method to measure seven common UV filters in fresh water and seawater.

A review was recently published by Gago-Ferrero *et al.* [127], which summarized LC-MS/MS methods for organic UV filters in the environment. UV filters included benzophenones, camphor derivatives, cinnamates, crylenes, benzimidazole derivatives, *p*-aminobenzoic acid and derivatives, dibenzoyl methane derivatives, salicylates, and triazines as well as their primary transformation products. In addition, their occurrence in river water, seawater, raw water, reclaimed water, sludge, river sediment, and biota is summarized.

11.4.2 UV-Filters as Endocrine Disrupters

Due to the lipophilic characteristics of UV filters, they can bioaccumulate and biomagnify through the food chain, and their presence is associated with estrogenic effects [128–130]. Most of the organic components in sunscreens are photostable and they can be easily absorbed by skin or orally and when absorbed can be partially metabolized [131]. These filters can also bioaccumulate in humans [128, 132]. Due to a high log octanol-water partition coefficient (log K_{ow}) of UV filters (3.8–5.9), these compounds are associated with high accumulation rates in fish [128, 133, 134]. Once a sunscreen compound is present in an organism's body at high concentrations, it can have many deleterious effects. In fish, various sunscreen agents have been found to be estrogenic, or able to mimic the hormone estrogen [135, 136].

Homosalate, benzophenones (-1, -2, and -3), butyl methoxydibenzoylmethane, ethylhexyl methoxycinnamate, 4-methylbenzylidene camphor, 3-benzylidene camphor, and ethylhexyl dimethyl PABA are considered to be a priority for further work based on their potential for affecting endocrine systems. All with the exception of butyl methoxydibenzoylmethane have been considered under the European Commission's strategy for endocrine disrupters.

Concerns on sunscreen agents have been raised from *in vitro* and *in vivo* studies carried out by Schlumpf *et al* on the estrogenicity of five sunscreen agents [137]. The five products tested were oxybenzone, homosalate (3,3,5-trimethylcyclohexyl 2-hydroxybenzoate, HMS), 4-methyl-benzylidene camphor (4-MBC), octyl-methoxycinnamate (OMC), and octyl-dimethyl-PABA (OD-PABA). According to these findings, UV screens should be tested for endocrine activity more extensively, in view of possible long-term effects on humans and wildlife.

Environmental levels of UV filters are not far below the doses that cause toxic effects in animals [118]. For example, sunscreen agents are a highly likely cause of coral bleaching. One study showed that in areas with high concentrations of sunscreen compounds coral bleaching was observed [138]. Oxybenzone, have been proven to promote viral infection in corals, resulting in bleaching [139].

Oxybenzone has also been shown to be a genotoxicant, a compound that damages DNA, as well as a phototoxicant, meaning its negative effects are worsened with the addition of sunlight [138]. These effects occur even at low concentrations.

The safety and efficacy of UV filters are regulated and approved by national and international health authorities. Safety standards in the EU, the United States, and Japan stipulate that new filters pass a stringent toxicological safety evaluation prior to approval. The safety dossier of a new UV filter resembles that of a new drug and includes acute toxicity, irritation, sensitization, phototoxicity, photosensitization, subchronic and chronic toxicity, reproductive toxicity, genotoxicity, photogenotoxicity, carcinogenicity, and, in the United States, photocarcinogenicity testing. Only substances with a safe toxicological profile and a margin of safety of at least 100-fold are approved for human use [140].

The biodegradation of UV filters has not been studied adequately and often varies in different chemical environments, and any degradation typically occurs over a longer period of time due to their UV-resistant nature [141]. The sunscreen agents that can be degraded by sunlight often result in the formation of free radicals capable of damaging DNA [142]. Based on the research data, the environmental safety of sunscreen agents remains unclear.

Of 16 UV filters approved by the USFDA, 9 are considered safe and effective either alone or in combination with other UV-filters based on extensive toxicologic evaluations [143]. However, nanoparticle physical sunscreen agents have been shown to cause DNA damage due to the production of free radicals [144].

The publicly available registration dossiers for the substance submitted under the EU REACH Regulation are available on the website of the European Chemical Agency (ECHA) [145]. They contain summaries of studies, many of them unpublished, submitted by industry in response to the standard data requirements of the REACH Regulation. A report has been filed prioritizing UV filters in cosmetics for environmental assessment [146].

The ECHA classification and labeling inventory² provides information on the classification and labeling of the substances in the EU. These provide an indication of the environmental hazard for the substance. It should be noted that for most of the substances, multiple entries exist, as suppliers have to notify the classification and labeling based on the information available to them.

11.4.3 UV Filters in the Environment

Because of their use in a wide variety of PCPs, these compounds can enter the aquatic environments by two primary routes: indirectly either through domestic water discharge during showering, bathing, or urine excretion or through WWTPs, or directly, by washing off from recreational activities such as swimming in oceans, lakes, and rivers and sunbathing on beaches, or through industrial wastewater discharge [118]. Because of their continuous release to the environment through these means, they can be considered as persistent pollutants [24].

² C & L Inventory Database. <http://echa.europa.eu> (accessed April 2017). European Chemical Agency.

UV filters and their transformation products enter the surfacewater [115, 123, 142, 147–149] and are considered to be a source of surface water contamination [133, 148, 149].

The rate at which sunscreen particles sediment or fall to the bottom of the water body varies for each compound [144]. Additionally, some compounds biodegrade faster than others (or some are not biodegradable). The concentration or the amount of sunscreen in water also typically increases with the population [150]. A study also found traces of sunscreen compounds in Arctic waters, indicating that the UV filters can even affect waters in which a very small number of people swim [150]. Several studies of freshwater rivers, basins, and lakes have found sunscreen compounds in both the water and sediment [151–153].

WWTPs are not very effective at removing these contaminants [124]. Several UV filters have been detected at ppb or ppt levels in surface water and wastewater, with maximum concentrations in summer time [148].

UV filters are not always stable under environmental conditions. Water in natural reservoirs is subjected to sun irradiation, while swimming-pool water is required to be disinfected by chlorination, bromination, ozonation, or UV-irradiation [131]. UV filters can undergo degradation and transformation to more toxic products. For example, Avobenzone undergoes transformation in the presence of chlorinated disinfection products and UV radiation to substituted chlorinated phenols and acetophenones, which are known for their toxicity [124].

They are lipophilic and tend to accumulate in the aquatic environments, soils, and sediments as well as in the food chain. Several studies have actually shown the presence of UV filters in aquatic organisms.

UV filters have rarely been monitored in groundwater [19, 154–156]. Trace levels of the compounds have been found in urban groundwater in the city of Barcelona (Spain). Maximum concentrations of 14 ng L^{-1} , 19 ng L^{-1} , 34 ng L^{-1} , and 37 ng L^{-1} were reported for 4-methylbenzylidene camphor, 2,4-dihydroxybenzophenone (BP1), oxybenzone, and benzophenone-4 (BP4), respectively [155, 156]. The only UV filter TP found in groundwater was BP1, which is a TP of oxybenzone.

As with PCs, the highest concentrations were observed in aquifer zones recharged by the river [156]. In addition, sewage network leaks have also been identified as a source of these compounds in groundwater [156]. Residues of octocrylene (8 ng L^{-1}) and BP3 (7 ng L^{-1}) have also been detected in groundwater impacted by MAR via injection of reclaimed water [19].

In lakes, the reported concentrations were in the range of $<2\text{--}35 \text{ ng L}^{-1}$ for BZ3, $<2\text{--}29 \text{ ng L}^{-1}$ for MBC, $<2\text{--}7 \text{ ng L}^{-1}$ for EMC, and $<20\text{--}24 \text{ ng L}^{-1}$ for BDM on cool days. On warm days, the concentration ranges increased up to $2\text{--}125 \text{ ng L}^{-1}$ for BZ3, $3\text{--}82 \text{ ng L}^{-1}$ for MBC, and $<2\text{--}15 \text{ ng L}^{-1}$ for EMC [148].

Although coastal tourism and recreation are the largest and most rapidly growing activities in the world, the evaluation of sunscreen from the perspective of chemical contamination of the coastal marine system has not been addressed. Concentrations of chemical UV filters included in the formulation of sunscreens, such as oxybenzone, 4-methylbenzylidene camphor (4-MBC), TiO_2 , and ZnO , have been detected in nearshore waters with variable concentrations over the

day mainly concentrated in the surface microlayer (i.e., 53.6–577.5 ng L⁻¹ BZ-3; 51.4–113.4 ng L⁻¹ 4-MBC; 6.9–37.6 µg L⁻¹ Ti; and 1.0–3.3 µg L⁻¹ Zn). The presence of these compounds in seawater suggests relevant effects on phytoplanktons [157].

The results from a study on Texas coastal zones in the Gulf of Mexico indicated that the county of Nueces has a high potential of water contamination through UV filters: EHMC: 477 kg yr⁻¹; OC: 318 kg yr⁻¹; BM-DBM: 258 kg yr⁻¹; and BP by 159 kg yr⁻¹ [158].

As in lakes, a similar trend was observed in seawater, where concentrations increased up to 8.2 ng L⁻¹ for BZ3, up to 19.7 ng L⁻¹ for MBC, and up to 10.7 ng L⁻¹ for EMC [159, 160]

Dissolution of sunscreens in seawater also releases inorganic nutrients (N, P, and Si forms) that can fuel algal growth. Results show that sunscreen products are a significant source of organic and inorganic chemicals that reach the sea with potential ecological consequences on the coastal marine ecosystem [157].

Fish have a strong tendency to accumulate UV filters [142, 161]. Reported concentrations of UV filters in fish ranged from 9 to 2400 ng g⁻¹ lipid weight [152]. The extensively used octocrylene (2-ethylhexyl-2-cyano-3,3-diphenyl-2-propenoate, OCT) was frequently found in the tissue liver of the Franciscana dolphin (*Pontoporia blainvillei*) at concentrations in the range of 89–782 ng g⁻¹ lipid weight [162]. These findings constitute the first data reported on the occurrence of UV filters in marine mammals worldwide.

UV filters have shown severe effects on coral reefs by bleaching corals at very low concentrations [139]. Recently, the UV filters were detected at concentration levels greater than 3700 ng L⁻¹ along the coastal areas of South Carolina in the United States [163].

11.4.3.1 Benzophenone Derivatives in the Environment

The use of benzophenone and some hydroxy benzophenone derivatives (see Figure 11.6) such as 2,4-dihydroxy benzophenone (BP-1), 2,2',4,4'-tetrahydroxy benzophenone (BP-2), 2-hydroxy-4-methoxy benzophenone (BP-3), 2,2'-dihydroxy-4-methoxy benzophenone, (BP-8), and 2,3,4-trihydroxy benzophenone (THB) in PCPs is because of their ability to absorb and to dissipate UVA light (400–315 nm).

BP-3 has been detected in water, soil, sediments, sludge, and biota but the highest detected level in ambient freshwater and seawater is 125 ng L⁻¹ and 577.5 ng L⁻¹, respectively, and 10,400 ng L⁻¹ in wastewater influent [134]. BP-3 is reported to be transformed into three major metabolites *in vivo*: BP-1, BP-8, and THB. BP-1 has a longer biological half-life than its parent compound and exhibits greater estrogenic potency *in vitro*.

Dietary studies on rats and mice where BP-3 was dermally and orally administered has shown that this compound affected body-weight gain, alterations in liver, kidney, and reproductive organs (see Figure 11.9) [164]. However, human exposure to BP-3 has not been associated with adverse health effects, and acute toxicity from BP-3 is low. The concentrations of BP-3 and other UV filters fluctuate significantly by location, levels of public access, season, and sampling conditions such as water depth or flow [165].

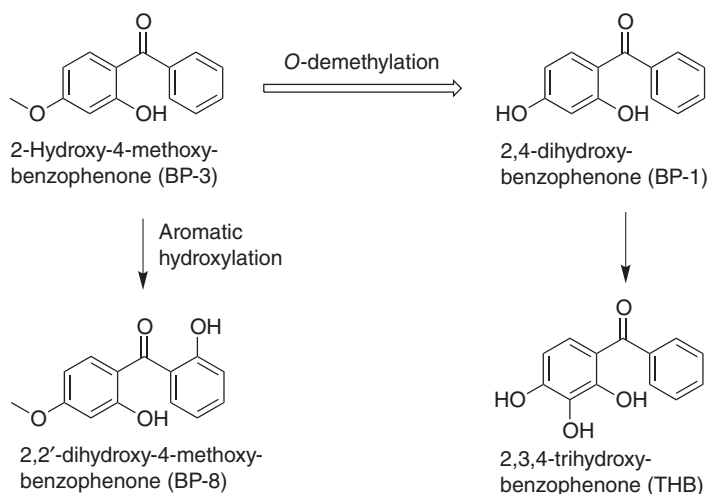


Figure 11.9 Metabolic pathways of benzophenone-3 in rats.

In river water in Korea, concentrations of 0.03–0.2 $\mu\text{g L}^{-1}$ for various benzophenone-type sunscreens have been detected as a result of industrial emissions [166].

11.4.3.2 3-Benzylidene- and 4-Methylbenzylidene-Camphor in the Environment

Concern about the hazards of 3-benzylidene-camphor (see Figure 11.7) is because this compound is under discussion. Although initially, its use as a component of sunscreens has been approved in Europe, in the United States the safety and efficacy of 3-benzylidene-camphor has not yet been reviewed for sunscreen use by the FDA, and therefore it cannot be employed in such products.

The controversy arises because of 3-benzylidene-camphor may be estrogenic as shown, for example, in *in vitro* and *in vivo* tests in fish [167]. The French Agency for the Safety of Health Products has announced that it will ban its use in cosmetics because some studies cite concerns over thyroid toxicity or hormone disruption. The Scientific Committee on Consumer Safety of EU in a report of 2013 considers that the use of 3-benzylidene-camphor as a UV-filter in cosmetic products in a concentration up to 2.0% is not safe due to its potential endocrine-disrupting properties and multiple hormonal activities reported *in vitro* as estrogenic and anti-estrogenic effects as well as anti-androgenic activities [168].

4-Methylbenzylidene-camphor (4-MBC) is another organic product of the camphor family used in sunscreen products to protect skin against UV radiation and may therefore help in the prevention of skin cancer. This product shows a low dermal absorption through human skin (<0.5% of dose), and *in vivo* tests have shown that, initially, 3-(4-carboxybenzylidene) camphor is formed from 4-MBC by a cytochrome P450, being the major metabolic product found in blood, whereas its glucuronide and 3-(4-carboxybenzylidene)-6-hydroxycamphor are the major metabolites in urine (see Figure 11.10).

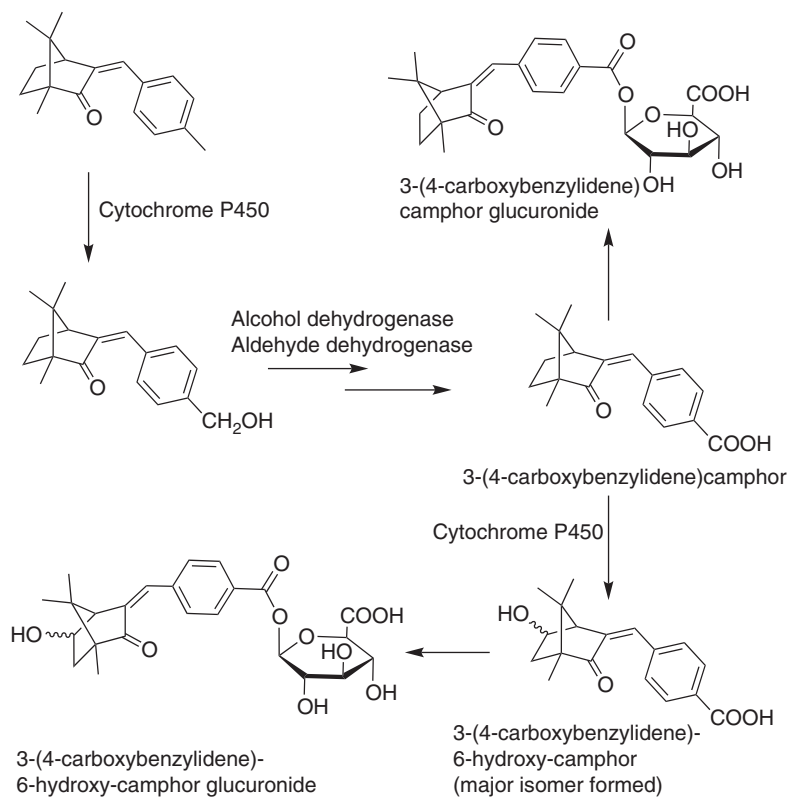


Figure 11.10 Metabolic pathway of 4-MBC *in vivo*.

Since 2001, 4-MBC has been investigated for its potential estrogenic activity in the reproductive system of fishes and rodents [137] and preliminary results on the estrogenicity of 4-MBC have raised concerns about their potential to act as an endocrine disruptor and provoke pituitary disorders comparable to hypothyroidism [169]. Although 4-MBC has been approved for use in Europe by the European Union's Scientific Committee for Cosmetic Products & Non-Food Products, in Canada, by Health Canada, it has been banned for use in Japan and in the United States by the FDA.

11.5 Insect Repellents: *N,N*-diethyl-*m*-toluamide (DEET)

Insect repellents³ are pesticides, as “pesticide” is a broad term that includes products that “don’t kill anything.” According to pesticide law, a pesticide is any substance or mixture of substances intended for:

- Preventing.
- Destroying.
- Repelling.

³ <https://www.epa.gov/insect-repellents/what-insect-repellent>.

- Mitigating any pest.⁴

Products labeled as repellents are not designed to eliminate pests. For example, in the case of skin-applied repellents, the product makes people less attractive to the pest. Insect repellents applied to the skin are often what we think of when we want to avoid insect bites. Other types of repellents that EPA registers include: Clip-on products that have a pad with the repellent and a fan or any other mechanism that disperses the repellent near your body. Spatial repellents use a heating mechanism to disperse the repellent in an outdoor area.

The following are active ingredients in EPA-registered skin-applied insect repellents:

- Catnip oil (*Nepeta cataria*, also known as catmint).
- Oil of citronella.
- DEET.
- IR 3535 (3-[*N*-butyl-*N*-acetyl]-aminopropionic acid, ethyl ester).
- Oil of lemon eucalyptus (*p*-menthane-3,8-diol).
- Picaridin.
- 2-undecanone (methyl nonyl ketone).

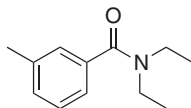
Recently, commercial repellent products containing plant-based ingredients have gained increasing popularity among consumers, as these are commonly perceived as “safe” in comparison to long-established synthetic repellents [170].

DEET is a chemical used in insect repellents that is applied directly to the skin in commercial products such as liquid sprays, lotions, or sticks to repel mosquitoes, ticks, chiggers, and other biting pests, but does not kill them [171].

DEET was originally developed by the U.S. Army in 1946 for use by military personnel in insect-infested areas (see Figure 11.11). It is used on humans to repel biting insects and ticks. Products such as sprays, creams, lotions, sticks, foams, and towelettes, containing from 4 to 100% of the active ingredient are applied directly to skin or clothing. There are also some products available for animal use [172]. Within the EU the use of DEET-based insect repellents may be regarded mainly as a way to avoid the annoyance of biting insects, but also to some extent as a way to minimize the spreading of Lyme disease (*Lyme borreliosis*) and meningitis.

Within the EU the maximum allowed concentration of DEET as an active ingredient in products is 20%. The corresponding annual use of DEET as an active component was 1800 t in 1990 [172, 173].

In pure manufactured form, the chemical is a clear, almost colorless, liquid with a mild characteristic odor. DEET has a water solubility of $<1 \text{ g L}^{-1}$ (at 20°C)



N,N-diethyl-*m*-toluamide (DEET)

Figure 11.11 Structure of *N,N*-diethyl-*m*-toluamide (DEET).

⁴ Mitigating means reducing the effect of something.

and low degree of volatilization (0.23 kPa vapour pressure). The log K_{ow} value indicates no potential for DEET to bioaccumulate.

There are conflicting data regarding the biodegradability of DEET. Since DEET is used mainly for direct application on the skin, a probable exposure route is through direct dermal absorption. Dermal absorption has been investigated in a study where undiluted technical grade DEET and 15% DEET in ethanol were applied on the skin of volunteers [174]. The mean uptake was 5.6% and 8.4%, respectively. Absorbed DEET was metabolized completely as no intact compound was found in the urine.

DEET has been detected in drinking water, ocean water, surface water, ground-water, and sewage water in various parts of the world [175]. Reported concentrations vary between 40 and 3000 ng L⁻¹ [175]. In a large survey of 59 selected compounds in 164 groundwater samples from 23 European countries, DEET was the organic pollutant with the highest frequency of detection and the highest concentration was 454 ng L⁻¹ [58]. However, the high prevalence in surface waters is contrary to the assumption that only relatively small amounts are used both within the Nordic countries and the EU and the fact that DEET is categorized as being readily biodegradable [176].

In the United States, one national water survey detected DEET in 75% of streams tested in 30 states, with median levels of 0.06 µg L⁻¹. An extensive study about the occurrence of a broad range of emerging contaminants in the groundwater in Africa, DEET was considered as “omnipresent,” at a median concentration greater than that observed in other groundwater studies across the globe [177]. In Sweden, DEET was not detected (limit of detection, $LOD = 2 \mu\text{g kg}^{-1}$ TS) in any of the four sludge samples from sewage-treatment plants. The compound was, however, detected in most of the incoming and in all of the outgoing water samples from the STPs (see Table 11.2) [173].

DEET is slightly irritating to the skin and clinical signs of neurotoxicity have been shown to occur in dogs after oral dosing [176]. However, DEET is considered by the USEPA as not classifiable as a human carcinogen. EPA has submitted a report, within the project Toxicity and Exposure Assessment for Children's Health (TEACH), which summarizes the scientific literature and U.S. federal regulations relevant to children's environmental health for some chemicals of special concern. Because of massive use, DEET and its derivatives have been incorporated into this project.⁵

11.6 Other PCPs

Using polymers, cosmetic chemists can create high-performance products. Broad-spectrums of polymers, namely, natural polymers, synthetic polymers, organic polymers as well as silicones are used in a wide range of cosmetics and PCPs such as film-formers, emulsifiers, thickeners, modifiers, protective barriers, and aesthetic enhancers [189].

⁵ <https://archive.epa.gov/region5/teach/web/html/index.html>.

Table 11.2 DEET concentration in different water types in countries.

Water source	Concentrations (ng L ⁻¹) (max or min–max)	Countries	[Ref.]
Influent sewage	<90–580	Sweden	[173]
	1500	Australia	[175]
	3000	Germany	[178]
Effluent sewage	9–700	Sweden	[173]
	60	Norway	[179]
	140	Australia	[175]
	1500	Germany	[178]
	2100	U.S.	[180]
Surface	2–1100	Sweden	[173]
	490	Australia	[175]
	30	Germany	[181]
	40	Netherlands	[182]
	1130	U.S.	[183]
	190	U.S.	[184]
	130	U.S.	[185]
	640	U.S.	[180]
Ground	<2–60	Sweden	[173]
	<0.4–454	EU	[58]
	13,000	U.S.	[186]
	30	Spain	[187]
Raw and treated drinking	8–13	U.S.	[188]
	3–270	U.S. and EU	[104]

Even within a certain class of polymers, the structural variations can also dictate what kinds of properties are found. Features such as the degree of polymerization, the amount of branching, and the ratio of the units within a copolymer can have a dramatic impact on the final performance attributes. A large number of thickeners, mostly polymers, are used in the cosmetic and personal care industry. They not only affect the rheological profile of the formulation but also influence application of the product, water sensitivity of the formulation, and delivery of the active ingredients.

Treated wastewater effluents are also known to contain plastic particles up to 100 particles L⁻¹ with current methods [190], including particles made from the same plastic type, which are also the same size and shape as particles applied in some PCCPs. Besides effluents, sewage sludge is another important receptacle of microplastics from PCCPs, with hundreds of particles kg⁻¹ ww typically detected there with current methods. Plastic particulates entering the environment, for example, via wastewater or biosolid runoff, can potentially be consumed as food by aquatic organisms and enter the food chain [191]. End-of-life plastic PCCP

ingredients are typically incapable of mineralizing at measurable rates in the environment, either by biodegradation or by photo- and/or thermal-degradation processes; estimates of half-lives run in the hundreds of years [192, 193], longer than any persistent organic pollutant.

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12

Water Disinfectant By-Products

12.1 Introduction

Water is vital to all living beings because it is essential for the creation and functioning of living cells. Water helps to shape our social and physical environment and thus water quality and location determine, to a great extent, human population centers, sources of energy, modes of transportation, and recreational activities.

In the past centuries, it was not known if water could contain bacteria and viruses that could cause disease and death. The WHO guidelines state:

“Infectious diseases caused by pathogenic bacteria, viruses, protozoa, and helminths are the most common and widespread health risk associated with drinking-water.” [[1], p. 118]

Drinking-water disinfection was a major public health achievement of the twentieth century. Before widespread disinfection of drinking water in many areas across the world, millions of people died from infectious waterborne diseases, such as dysentery, typhoid, gastroenteritis, and cholera. However, following the use of chemical disinfection, that began in the early 1900s, deaths attributable to these waterborne pathogens virtually ceased in developed nations.

In disinfection, gaseous chlorine (Cl_2) or liquid sodium hypochlorite (bleach, NaOCl) is added to water to form hypochlorous acid (HClO). In 1974, Rook [2] discovered that HClO and hypobromous acid (HBrO) also react with naturally occurring organic matter to create many water DBPs. This led to research on other chemicals formed when chlorine is added to water, and to the health effects of these chemicals.

Richardson [3] described the DBP formation and occurrence in drinking water. A comprehensive listing of >600 DBPs identified from different disinfectants and disinfectant combinations is provided, and a discussion on the formation and occurrence, issues with alternative disinfectants, route of exposure, and formation of “pollutant” DBPs is included [4].

Krasner *et al.* [5] published a review on the formation, precursors, control, and occurrence of nitrosamines in drinking water. Bond *et al.* [6] reviewed the precursors of *N*-DBPs in drinking water, discussing precursors of haloacetonitriles, haloacetamides, halonitromethanes, nitrosamines, and cyanogen halides.

12.2 Wastewater Treatments

Each time water is used to wash our bodies, clothes, and cars, or to cook food or brush our teeth, wastewater is produced. Each time an industry uses water to make paper products, iron, steel, and oil, wastewater results. Wastewater can be defined as all the used water generated by a community, including human waste flushed down toilets, food scraps washed down sinks, and the water from washing machines, bathtubs, and street storm drains and businesses of all kinds. Wastewater, also called sewage, is about 99.94% water and only 0.06% of actual waste.

The wastewater treatment process (see also Chapter 2.) can vary slightly from plant to plant, but typically involves the following steps:

- Preliminary treatment.
 - 1) Wastewater flows by gravity into the plant.
 - 2) Wastewater is pumped through screens to remove large debris, for example, sticks and rags.
 - 3) Wastewater then flows through basins at a speed that allows heavy inorganics, for example, sand and gravel, to settle.
- Primary treatment.
 - 1) Wastewater flows slowly through primary sedimentation tanks where solids that are heavier than water sink to the bottom, as the water continues to flow.
 - 2) Scum and grease that float to the top are skimmed off.
 - 3) The solids that have settled to the bottom, called sludge, are scraped out, concentrated, and converted to fertilizer.
- Secondary treatment.
 - 1) Wastewater is combined with activated sludge, sludge containing the same microorganisms that decompose sewage in nature, to consume the remaining dissolved and suspended solids in the wastewater.
 - 2) Pure oxygen is added to promote an oxygen-rich atmosphere and to encourage the microorganisms to consume the wastes. The addition of oxygen ensures that the microorganisms will not consume all the oxygen in the water as they consume the wastes.
 - 3) These microorganisms become fat and heavy after consuming the waste and drop to the bottom of the final settling tanks where they are either scraped out and converted to fertilizer or recycled to feed over and over again on additional wastes.
 - 4) The water is mixed with enough chlorine to kill any remaining disease-producing organisms and returned to the river.

WWTPs speed up the natural processes by which water is cleaned. In the natural process, bacteria and other microscopic organisms, for example, algae, fungi, protozoa, in a stream or river, are attracted to the pollutants in the wastewater as a source of food. In addition to using these same microscopic organisms in the wastewater treatment process, WWTPs use physical methods of screening and gravity settling to remove debris and other pollutants.

12.2.1 Water Reuse

The use of reclaimed water for non-potable purposes¹ is widely accepted and is developing rapidly worldwide. At present, in Europe there is no imperative for the use of reclaimed water for potable purposes. There are still adequate surface water sources available to meet the short- to medium-term needs of our major urban centres. Nevertheless, of all the forms of reuse available in the major urban areas, potable reuse could well be the most cost-effective in the long-term.

It is predicated on a number of straightforward assumptions:

- Direct potable reuse will necessitate stringent wastewater source control to minimize the risk of contamination; nevertheless, given the increasing need to improve effluent quality for environmental protection, it is considered that source control requirements are only likely to become more stringent in the future, with or without potable reuse.
- The extent of treatment required for full direct potable reuse is likely to represent a marginal increase in the overall cost of the wastewater-treatment process.
- Because it would distribute water through the existing water supply system, direct potable reuse would require very limited additional distribution and storage infrastructure.
- Potable reuse has the capacity to readily utilize all the wastewater generated; water demand will always be greater than the wastewater supply because the wastewater flow to the treatment facility is a subset of the total potable water use.

It is considered inevitable that, in time, potable reuse in some form will occur.

12.2.2 Drinking Water Treatments

The drinking water treatment process involves the following steps:

- 1) Screening to remove debris.
- 2) Natural sedimentation in reservoirs during which large particles settle to the bottom.
- 3) The addition of chemicals, which causes smaller particles to clump together and settle to the bottom.
- 4) Filtration during which the very tiny particles are removed.
- 5) Addition of fluoride for teeth protection.
- 6) Disinfection (usually chlorination) to destroy disease-causing bacteria.

12.2.3 Water Disinfection

Regardless of the method employed, disinfection is only one of the requirements of a potable-water supply system. Disinfection requirements and efficacy are often highly interrelated with other water-supply and treatment operations. A complete system of potable-water supply operations may be considered in three general phases: collection, treatment, and distribution.

¹ Irrigation of agriculture and open urban areas, and other non-potable urban uses.

The natural environment contains numerous microorganisms, most of which present no concerns. However, some are extremely harmful and therefore disinfection is vital. Disinfection methods include chlorination, ClO_2 , NH_2Cl , O_3 , and UV light.

Disinfection is the key step in making drinking water safe. Theoretically, disinfection can be either physical or chemical. Disinfectants must kill microorganisms when used but also have a persistent effect until they arrive at houses for preventing contamination with pathogenic microorganisms during distribution.

Recent serious outbreaks of waterborne illness² have served as dramatic reminders of the need for proper disinfection and control of waterborne pathogens in drinking water, suggesting that there is a need for continual reevaluation of disinfection techniques to ensure effective drinking-water disinfection.

12.3 Disinfection Methods

Disinfection can be performed by physical or chemical means. The most widely used chemical disinfectants are chlorine (Cl_2), ozone (O_3), chlorine dioxide (ClO_2) and chloramine (NH_2Cl). The chemical disinfectants are all water-soluble oxidants, which are produced either onsite (e.g., O_3) or offsite (e.g., Cl_2). They are administered as a gas (e.g., O_3 , Cl_2) or liquid (e.g., hypochlorite) at typical doses of several mg L^{-1} , either alone or in combination. In addition, UV irradiation or other oxidation reactions induced by radiation are also used.

Cl_2 , a strong oxidant, has been widely used throughout the world as a chemical disinfectant, serving as the principal barrier to microbial contaminants in drinking water. Chlorination has been the major disinfectant process of municipal drinking water in many countries for years despite the availability of alternative disinfectants such as O_3 , ClO_2 , and chloramines (NH_2Cl) [7].

The noteworthy biocidal attributes of Cl_2 have been somewhat offset by the formation of DBPs during the chlorination process. As a consequence, alternative chemical disinfectants are increasingly being used. However, each has been shown to form its own set of DBPs. The physicochemical properties of disinfectants and DBPs can affect their performance in drinking water, as well as their toxicology and epidemiology.

12.3.1 Chlorination

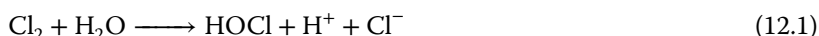
Cl_2 was discovered in 1774 by the chemist K. Scheele. One of the first known uses of Cl_2 for disinfection was not until 1850, when Snow used it to attempt to disinfect London's water supply during that now-famous cholera epidemic. It was not until the early 1900s, however, that chlorine was widely used as a disinfectant. Cl_2 revolutionized water purification, reduced the incidence of waterborne diseases across the Western world, and "chlorination and/or

2 *Escherichia coli* induced gastroenteritis in Walkerton, Ontario, Canada, in 2000, cryptosporidiosis in Milwaukee, Wisconsin, U.S., in 1993, and cholera in Peru in 1991.

filtration of drinking water has been hailed as the major public health achievement of the twentieth century.” [8]

Cl_2 is an effective microbiocide against most waterborne pathogens. It is inexpensive and relatively easy to produce, store, transport, and use. Cl_2 is applied to water in one of three forms: elemental chlorine (chlorine gas), Cl_2 , hypochlorite solution (bleach), NaClO , or dry calcium hypochlorite, $\text{Ca}(\text{ClO})^2$. All three of these forms produce free chlorine in water.

Elemental chlorine is the most commonly used form of Cl_2 , which is transported and stored as a liquefied gas under pressure. NaClO , or bleach, is produced by adding elemental chlorine to sodium hydroxide NaOH . Typically, hypochlorite solutions contain from 5 to 15% of Cl_2 . It is easier to handle than gaseous Cl_2 or $\text{Ca}(\text{ClO})^2$. $\text{Ca}(\text{ClO})^2$ is a white solid that contains approximately 65% of Cl_2 and dissolves in H_2O . It is a very stable but corrosive material with a strong odor that requires proper handling. Its solubility makes it easy to apply in controlled amounts either as Cl_2 gas, which readily dissolves in water at room temperature, or as a salt of hypochlorite, which is formed by the reaction of Cl_2 and H_2O as follows:



In disinfection, Cl_2 or liquid NaClO is added to, and reacts with, H_2O to form (HClO). During chlorination, the relative concentrations of the hypochlorous acid (HClO) and hypochlorite ions (ClO^-), together termed “free chlorine,” are determined mainly by measurement of pH. HClO , a more effective biocide than ClO^- , dissociates into ClO^- between a pH of 7.0 and 8.0, the range in which most potable water undergoes treatment.

A typical concentration of free available chlorine used for the treatment of drinking water is 1.0 mg L^{-1} . Drinking water becomes increasingly unpalatable as concentrations of free chlorine rise above this level.

Cl_2 in the form of hypochlorous acid/hypochlorite ion (HClO/ClO^-) reacts with bromide ion (Br^-), oxidizing it to hypobromous acid/hypobromite ion (HBrO/BrO^-). HClO (a more powerful oxidant) and hypobromous acid (HBrO) (a more effective halogenating agent) react collectively with natural organic matter, such as humic and fulvic acids, to form a wide range of halogenated organic compounds, which were first reported 40 years ago [2]. These halogenated organic compounds include trihalomethanes (THMs), haloacetic acids (HAAs), haloacetonitriles (HANs), haloketones, chloral hydrate, and chloropicrin.

Another reaction that occurs with Cl_2 is the formation of chlorate (ClO_3^-) in concentrated hypochlorite solutions.

12.3.2 Chlorine Dioxide

Chlorine dioxide (ClO_2) is generated onsite, by a mixture of sodium chlorite (NaClO_2) and elemental Cl_2 in solution. In solution it is a dissolved gas.



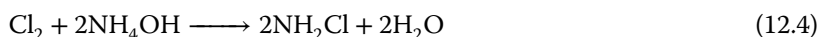
It is a faster-acting disinfectant than elemental Cl_2 and it is a selective oxidant, which neither forms chlorinated by-products (THMs, HAAs), nor oxidizes Br^-

to Br_2 , and it is more effective than Cl_2 in treating certain taste and odor problems. It is used mainly as an industrial bleaching agent. It is unstable, sensitive to temperature and light, and explosive in air at concentrations of about 4% or more.

The major ClO_2 DBPs include chlorite (ClO_2^-) and chlorate (ClO_3^-) ions, with no direct formation of organohalogen DBPs. Unlike the other disinfectants, the major ClO_2 DBPs are derived from the decomposition of the disinfectant as opposed to reaction with precursors.

12.3.3 Chloramination

Chloramines NH_2Cl are formed when water containing ammonia is chlorinated or when ammonia (NH_3) is added to water containing Cl_2 (ClO^- or HClO) (see Eq. (12.4)).



It is an effective bactericide that produces fewer DBPs. It is a weak disinfectant and oxidant, and it is much less effective against viruses and protozoa than elemental Cl_2 . It is almost never used as a primary disinfectant, and it does not oxidize Br^- to Br_2 . It is more stable as a residual, and has less taste and odor than does free Cl_2 .

Chloramination has become a widely used alternative to chlorination, and as a secondary disinfectant generally leads to the formation of cyanogen chloride (CNCl), a nitrogenous compound, which significantly reduces levels of chlorine DBPs. A related issue is the presence of nitrite (NO_2^-) in chloraminated distribution systems.

12.3.4 Sodium Dichloroisocyanurate

Sodium dichloroisocyanurate, the sodium salt of a chlorinated hydroxytriazine, is used as a source of free available chlorine (in the form of hypochlorous acid, HOCl) for disinfecting drinking water (see Figure 12.1).

Sodium dichloroisocyanurate can be manufactured either as the anhydrous salt or as the dihydrate. Anhydrous sodium dichloroisocyanurate contains about 63% free available chlorine. When this compound is added to water, it is rapidly hydrolyzed to release free available chlorine, establishing a complex series of equilibria involving six chlorinated and four non-chlorinated isocyanurates. As free available chlorine is consumed on reacting with organic material in the water, chloroisocyanurates rapidly dissociate and continue to release free chlorine.

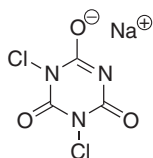


Figure 12.1 Chemical structure of sodium dichloroisocyanurate.

Sodium dichloroisocyanurate (NaDCC)

The use of sodium dichloroisocyanurate as a source of freely available chlorine is not expected to lead to greater production of by-products than does the use of elemental chlorine.

12.3.5 Ozonization

Ozone (O_3), an allotrope of O_2 having three atoms to each molecule, is formed by passing dry air through a system of high voltage electrodes. It is one of the strongest oxidants and disinfectants available. It has high reactivity and low solubility. However, its virtues make it difficult to apply and control because this gas is unstable and must be generated onsite. Normally, a secondary disinfectant is required because O_3 does not maintain an adequate residual in water. Rather, it forms brominated (bromate, brominated organics) and non-halogenated by-products (ketones, organic acids, and aldehydes). In addition, it breaks down more complex organic matter into smaller compounds that can increase DBP formation during the secondary disinfection process.

In comparison with chlorination, ozonation has the advantage that it renders viruses inactive. In addition, it does not affect the taste of the water. Ozonation can have undesirable side effects: for example, toxic products of oxidation can emerge and organic compounds containing nitrogen release NO_3^- by oxidation. Also, O_3 can directly or indirectly react with bromide to form brominated ozone DBPs, including bromate ion (BrO_3^-). In the presence of natural organic matter (present in $mg\ L^{-1}$ level) (NOM), non-halogenated organic DBPs, such as aldehydes, ketoacids, and carboxylic acids are formed during ozonation, with aldehydes (e.g., formaldehyde) being dominant. If both NOM and bromide are present, ozonation forms hypobromous acid, which, in turn, leads to the formation of brominated organohalogen compounds (e.g., bromoform).

12.3.6 UV Irradiation

UV radiation, generated by mercury arc lamps, is a non-chemical disinfectant. When UV radiation penetrates the cell wall of an organism, it damages genetic material and prevents the cell from reproducing. UV radiation effectively destroys bacteria and viruses. As with O_3 , a secondary disinfectant must be used to prevent the regrowth of microorganisms. It produces no known toxic residuals, requires short contact times, and the equipment is easy to operate and maintain.

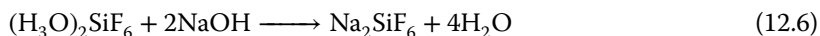
The use of UV irradiation for primary disinfection is mainly due to the need for some systems to inactivate *Cryptosporidium* [9, 10]. At UV dosages used for microbial inactivation, there has typically been no evidence that UV irradiation affects (increases or decreases) DBP formation [11].

Increased use of UV irradiation as a primary disinfectant is likely to continue, thus reducing reliance upon O_3 or free chlorine, and, it is hoped that it will reduce the overall DBP formation in water delivered to the public.

12.3.7 Other Methods of Disinfection

Water fluoridation is used, by addition of fluoride, with the goal of preventing tooth decay. Generally, fluoridation is accomplished by the addition of

hexafluorosilicic acid, $(\text{H}_3\text{O})^2\text{SiF}_6$, which decomposes in H_2O , yielding F^- ions. Neutralization of solutions of hexafluorosilicic acid with alkali bases produces the corresponding alkali metal fluorosilicate salts. The resulting salt Na_2SiF_6 is used mainly in water fluoridation (see eqs. 12.6 and (12.7)). Near neutral pH, hexafluorosilicate salts hydrolyze rapidly according to the following scheme [12]:



Water with high concentrations of hard salts can be treated with soda ash (sodium carbonate, Na_2CO_3) which precipitates out the excess salts producing calcium carbonate (CaCO_3). *In situ* chemical oxidation is accomplished by injecting or otherwise introducing strong oxidizers directly into the contaminated medium to destroy chemical contaminants in place. It can be used to remediate a variety of organic compounds, including some that are resistant to natural degradation.

12.4 Water DBPs

DBPs are formed upon the reaction of chemical disinfectants with DBP precursors. NOM, commonly measured by total organic carbon, serves as the organic precursor, whereas bromide ion (Br^-) serves as the inorganic precursor. Dissolved organic matter in fresh waters typically constitute over 80% of the total organic matter in fresh waters [13], and are considered the most organic precursors of DBPs.

NOM is a complex mixture of substances, such as humic acids, fulvic acids, amino acids, carbohydrates, lipids, lignins, waxes, and organic acids. Fulvic and humic acids have been shown to be the primary precursor materials for the formation of DBPs [14, 15].

The reaction between the disinfectant and NOM occurs because most disinfectants used for treating drinking water are also powerful oxidants; they oxidize (and some also halogenate) NOM.

Studies have suggested that the formation of DBPs during the chlorination of drinking water is influenced by disinfection processes and chemicals, removal of NOM before the point of disinfectant application, prior addition of disinfectant, water source, pH, temperature, concentration of chlorine residual, residence time, reaction time, total organic carbon, and bromide content [16–22].

The DBPs are measurable by gas or liquid chromatography and can be classified as organic or inorganic, halogenated (chlorinated or brominated) or non-halogenated, and volatile or non-volatile. Upon their formation, DBPs can be stable or unstable (e.g., decomposition by hydrolysis). In 1974, Rook [2] reported on the identification of the first DBPs—chloroform and the other THMs that are formed in chlorinated drinking water.

12.4.1 DBPs from Chlorination

The added chlorine³ reacts with naturally occurring organic matter to form a wide range of halogenated organic compounds. These compounds, referred

³ As hypochlorous acid and hypobromous acid.

Table 12.1 Examples of halogenated DBPs reported for chlorination.

DBPs	Examples
Trihalomethanes	Chloroform, bromodichloromethane, bromochloroiodomethane
Other haloalkanes/alkenes	Dibromomethane, pentachloropropene
Halomonocarboxylic acids	Trichloroacetic acid, dichloro-hydroxy-benzoic acid
Halodicarboxylic acids	Chloro-hydroxy-dicarboxylic acid
Halotricarboxylic acids	2-Chloro-3-dicarboxy-2-butenic acid
MX and analogs	3-Chloro-4-(dichloromethyl)-5-hydroxy-2(5 <i>H</i>)-furanone (MX), (<i>E</i>)-2-chloro-3-(dichloromethyl)-4-oxobutenoic acid (EMX)
Haloketones	1,1,1-Trichloropropanone
Halonitriles	Dichloroacetoneitrile, cyanogen chloride
Haloaldehydes	Trichloroacetaldehyde
Haloalcohols	Chloroisobutanol
Haloamides	2,2-Dichloroacetamide
Haloesters	1-Chloroethanol acetate
Halophenols/aromatics	2-Chlorophenol, chlorobenzene
Halonitromethanes	Trichloronitromethane
Halothiophenes	Tetrachlorothiophene

to as DBPs (see Table 12.1), include the four primary THMs or TTHM (for total trihalomethanes): chloroform (CHCl_3), bromodichloromethane (CHCl_2Br), dibromochloromethane (CHClBr_2), bromoform (CHBr_3), HANs, haloketones (HKs), haloaldehydes, haloalcohols, haloamides, halonitromethanes, chloropiricin, halogenated acetic acids,⁴ [23] and non-halogenated chemicals, such as carboxylic acids, aldehydes, and ketones [24]. Table 12.1 lists examples of DBPs that have been identified for chlorine disinfection.

The dominance of chlorine DBP groups generally decreases in the order of THMs, HAAs, and HANs. The relative amounts of total organic carbon, bromide, and chlorine will affect the species distribution of THMs, HAAs, and HANs. Generally, chlorinated THM, HAA, and HAN species dominate over brominated species, although the opposite may be true in high-bromide waters. Although many specific chlorine DBPs have been identified, a significant percentage of the total organic halogens still remain unaccounted for.

Over the past 40 years, more than 500 DBPs have been identified [24]. The identification of unknown DBPs continues to be important because more than 50% of the total organic halide (TOX) formed in chlorinated drinking water remains unknown. Similarly, over 60% of the assimilable organic carbon (AOC) formed in ozonated drinking water also remains unknown [4]. Relative amounts of ozone and chlorinated DBPs, as AOC and as TOX, respectively, in water are illustrated in Figure 12.2 [4].

4 HAAs, up to nine chlorinated/brominated species.

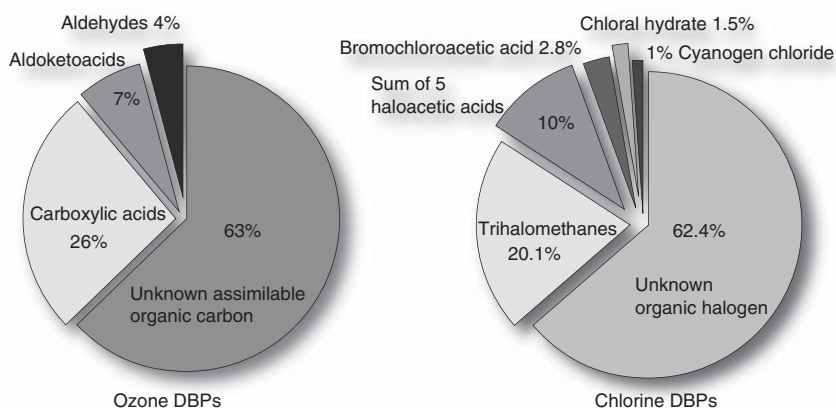


Figure 12.2 Relative amounts of ozone and chlorinated DBPs in drinking water.

Contaminant DBPs have been recently reported from pesticides, PCs, antibacterials, PCPs, and musks. Some of this research has been conducted in an effort to find ways to degrade and remove these contaminants from wastewater effluents and drinking-water sources, but some of this research is being conducted to determine the fate of these contaminants in drinking water treatment.

Studying DBP formation in chlorinated drinking water, Pan and Zhang [25] discovered aromatic DBPs, which were classified into four groups: dihalo-4-hydroxybenzaldehydes, dihalo-4-hydroxybenzoic acids, dihalo-salicylic acids, and trihalo-phenols.

12.4.2 Other Halogenated DBPs

Newer DBPs of emerging concerns include brominated and iodinated compounds, such as bromonitromethanes, iodo-trihalomethanes, iodo-acids, and brominated forms of 3-chloro-4-(dichloromethyl)- 5-hydroxy-2(5H)-furanone or mutagen-X (MX) (see Figure 12.3).

The DBP MX is present in a ring-opened oxo-butenic acid form at the pH of drinking water (see Figure 12.4). The identification of this potent mutagen eluded researchers for quite some time because of its low concentration and its polarity. It was originally identified in pulp-mill effluent [26] but was later found in chlorinated drinking water from a number of samples taken around the world [27–30]. Other analogs of MX were also later identified in chlorinated drinking water, including its isomer, EMX [29, 30], oxidized and reduced forms of MX (ox-MX and red-MX) [31], as well as brominated analogs (BMXs) (see Figure 12.3) [32].

Iodinated THMs are responsible for medicinal taste-and-odor problems in drinking water [33], and iodinated acids have been detected in waters containing iodide. Because of their potential health risks, their occurrence and formation in drinking water have been studied [34]. Karpel Vel Leitner *et al.* [35] reported that ammonia and organic amines enhanced iodoform formation in chlorinated water containing iodide. Bichsel and von Gunten [36] investigated iodinated THMs formation in chlorinated, chloraminated, and ozonated waters. This study indicated that the oxidation of iodide to hypiodous acid (HOI) increased in the

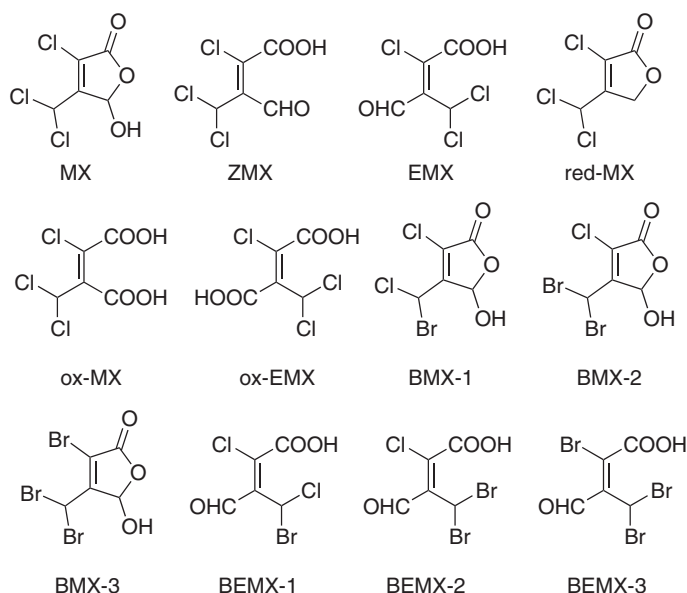
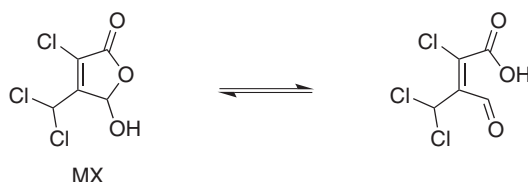


Figure 12.3 Structure of mutagen-X (MX) and analogs.

Figure 12.4 MX ring opening equilibrium reaction (pH driven).



order of $O_3 > Cl_2 > NH_2Cl$. Moreover, ozone and chlorine, but not chloramines, could further rapidly oxidize HOI to iodate, which would be a sink for the iodide (I^-) and, thus, would be unavailable for forming iodinated organic DBPs. Alternatively, in chloraminated waters, HOI could react with NOM to form iodinated DBPs. Hua *et al.* [37] reported the effect of iodide on the formation of iodinated DBPs and found that the Cl_2 :total organic carbon or Cl_2 : I^- ratio was critical to the formation of iodinated DBPs. They proposed a strategy to control the formation of iodinated DBPs in drinking water, by utilizing an appropriate dose of chlorine to convert the majority of iodide to iodate and then adding ammonia to form chloramines for distribution residual maintenance. Finally, Hua and Reckhow [38] demonstrated that iodinated DBPs could form during chlorine dioxide treatment.

In 2011, Duirk *et al.* [39] discovered the formation of highly toxic DBPs (iodo-acids and iodo-THMs) when iodinated X-ray contrast media are treated with chlorine or chloramines.

12.4.3 Nitrogenous DBPs

Nitrogenous DBPs have attracted much attention because chloramination favors the formation of certain nitrogenous DBPs; for example, cyanogen chloride [40]

Table 12.2 Examples of DBPs reported for Cl₂ and O₃.

Compound	Formula	Compound	Formula
Oxidation by-products		Miscellaneous chlorinated organic compounds	
Trichloroacetamide	CCl ₃ – CONH ₂	Chloral hydrate	CCl ₃ – CH(OH) ²
Chloroacetaldehyde	CClH ₂ – CHO	Chloropicrin	CCl ₃ – NO ₂
THMs		Cyanogen halides	
Chloroform	CHCl ₃	Cyanogen chloride	Cl [–] –CN
Bromodichloromethane	CHBrCl ₂	Cyanogen bromide	Br [–] –CN
Dibromochloromethane	CHBr ₂ Cl	Oxyhalides	
Bromoform	CHBr ₃	Chlorite	ClO ₂ [–]
HAAs		Chlorate	ClO ₃ [–]
(Mono)chloroacetic	CH ₂ Cl–COOH	Bromate	BrO ₃ [–]
Dichloroacetic	CHCl ₂ – COOH	Aldehydes	
Trichloroacetic	CCl ₃ – COOH	Formaldehyde	H – CHO
Bromochloroacetic	CHBrCl–COOH	Acetaldehyde	CH ₃ – CHO
Bromodichloroacetic	CBrCl ₂ – COOH	Glyoxal	CHO – CHO
Dibromochloroacetic	CBr ₂ Cl–COOH	Methyl glyoxal	CH ₃ – CO – CHO
(Mono)bromoacetic	CH ₂ Br–COOH	Aldoketo acids	
Dibromoacetic	CHBr ₂ – COOH	Glyoxylic acid	CHO – COOH
Tribromoacetic	CBr ₃ – COOH	Pyruvic acid	CH ₃ – CO – COOH
HANs		Ketomalonic acid	HOOC – CO – COOH
Dichloroacetonitrile	CHCl ₂ – CN	Carboxylic acids	
Trichloroacetonitrile	CCl ₃ – CN	Formate	H – COO [–]
Bromochloroacetonitrile	CHBrCl–CN	Acetate	CH ₃ – COO [–]
Dibromoacetonitrile	CHBr ₂ – CN	Oxalate	– OOC – COO [–]
Haloketones (HKs)		Maleic acids	
1,1-Dichloroacetone	CHCl ₂ – CO – CH ₃	2-tert-Butylmaleic acid	
(propanone)			
1,1,1-Trichloroacetone	CCl ₃ – CO – CH ₃		
(propanone)			

and *N*-nitrosodimethylamine (NDMA) [41]. Among the nitrogenous DBPs, NDMA has been extensively studied. In addition, halonitromethanes (HNMs) and haloacetamides are emerging nitrogenous DBPs on which new research has been conducted (see Table 12.2).

Dibromonitromethane is formed by treatment with chlorine or chloramine as well as by treatment with O₃/Cl₂ and O₃/NH₂Cl [42]. The identification of dibromo-nitromethane was reported in 1999 [42], and it has been shown to be extremely cytotoxic and genotoxic to mammalian cells [43].

NDMA is a contaminant originating from rocket fuel, plasticizers, polymers, batteries, and other industrial sources. It was discovered to form as a DBP in

waters treated with NH_2Cl or Cl_2 . NDMA is listed as a probable human carcinogen and might be more widespread than previously believed, because of its formation as a DBP in drinking water.

Similar to trihalohaloketones, trihaloacetaldehydes, and brominated trihaloacetic acids, and some nitrogenous DBPs, such as haloacetonitriles and cyanogen chloride, can undergo base-catalyzed hydrolysis. Alkaline hydrolysis of haloacetonitriles can form haloacetamides, and ultimately HAAs.

Yang *et al.* [44] investigated various monochloramine application modes on the formation of various nitrogenous DBPs. Good linear relationships were found between monochloramine dosage and dichloroacetonitrile and cyanogen chloride formation. However, the chloramination modes had little effect on the formation of dichloroacetonitrile and cyanogen chloride.

Schreiber and Mitch [45] highlighted the critical importance of dichloramine and dissolved oxygen in nitrosamine formation. Lee *et al.* [46] reported on the destruction or transformation of NDMA precursors using O_3 and ClO_2 , and Krasner *et al.* [5] found treated wastewater to be a major source of NDMA precursors. Some cationic polymers contain NDMA precursors, and therefore it is important not to overdose the polymers used in the coagulation process [47]. Preozonation was found to increase the formation of certain HNMs during post-disinfection [48].

Chloropicrin formation was greatly enhanced by medium-pressure UV, possibly due to photo-nitration. Moreover, nitrite was found to be a potential source of nitrogen in the nitro group of chloropicrin. Haloacetamides were found to be present at levels similar to other commonly measured DBPs [48]. One particularly remarkable discovery in this regard was the formation of high levels of NDMA in drinking water that resulted from the reaction of O_3 with a fungicide (tolylfluanide) used in Europe [49].

12.4.4 Carbonaceous DBPs from Ozonation

Emerging carbonaceous DBPs include haloaldehydes and halogenated furanones (see Table 12.2), in addition to other non-halogenated DBP that are formed (see Table 12.3). Ozonation and chloramination controlled the formation of chloral hydrate (trichloroacetaldehyde). However, this treatment process increased the formation of dihaloaldehydes. It has been shown that acetaldehyde (an ozone DBP) can react with chlorine to form chloral hydrate, whereas acetaldehyde reacted with chloramines and formed dihaloaldehydes. However, it should be possible to minimize the formation of haloaldehydes at ozone plants through the use of biological filtration. Many water facilities in the United States have been considering using chloramination to reduce the levels of regulated carbonaceous DBPs in their water [50].

12.5 Methods of Analysis of DBPs

In any given extract, there may be as many as 300 compounds that are detected. Many of these will be naturally occurring compounds or pollutants that were already present in the source water prior to disinfection, and many will be DBPs.

Table 12.3 Examples of non-halogenated DBPs.

DBPs	Examples
Mono- and dicarboxylic acids	Hexanoic acid, propanedioic acid, benzoic acid
Heterocyclic carboxylic acids	5-methyl-2-furancarboxylic acid
Cyano-carboxylic acids	3-Cyanopropanoic acid
Nitriles	Benzeneacetonitrile
Phenols/aromatics	Methylphenol, benzene
Aldehydes	Formaldehyde, benzaldehyde

GC/MS allowed researchers to separate complex mixtures and identify the individual pollutants. The individual compounds are separated on the column and elute through the column into the mass spectrometer, where they are ionized and analyzed [51]. Typical GC/MS analyses use only one type of MS: low-resolution electron ionization (EI). High-resolution MS can be coupled to GC to obtain exact mass data for the unknowns, which can provide the empirical formula for the unknown structure and empirical formula information for the fragments of the molecule. GC-IR spectroscopy can also be used in addition to GC/MS to determine functional-group information in the molecule. When molecular ions are missing, another ionization technique, chemical ionization (CI)-MS, can be used to generate a pseudo-molecular ion. CI-MS involves the initial electron ionization of a gas, such as methane, isobutane, or ammonia. The identification of dibromo-nitromethane and MX, is a classic example of how MS and GC/MS have been used to identify DBPs (see Section 12.4.3).

Although GC/MS has been and continues to be the most effective analytical technique for identifying unknown DBPs in drinking water, its use is limited to the lower-molecular-weight fraction of DBPs. As the molecular weight of a molecule increases, it generally becomes less volatile and less amenable to GC. Another limitation involves ionic, highly polar, hydrophilic compounds, which are not amenable to direct analysis by GC/MS. They are generally either very difficult or impossible to extract from water.⁵ One way to overcome these obstacles is through derivatization of the polar DBP and subsequent GC/MS analysis.

Another way to analyze hydrophilic DBPs in drinking water is with the help of LC/MS. ESI and atmospheric-pressure chemical ionization (APCI) are currently the most effective ionization techniques being used with LC/MS, permitting detection of the hydrophilic DBPs at the lowest limits. Studies involving the identification of unknown DBPs by LC/MS have also employed derivatization, using dinitrophenylhydrazine (DNPH) and 4-dimethylamine-6-(4-methoxy-1-naphthyl)-1,3,5-triazine-2-hydrazine (DMNTH) [4] (see Figure 12.5).

⁵ Extraction into an organic solvent is necessary for GC/MS analysis because water cannot be used.

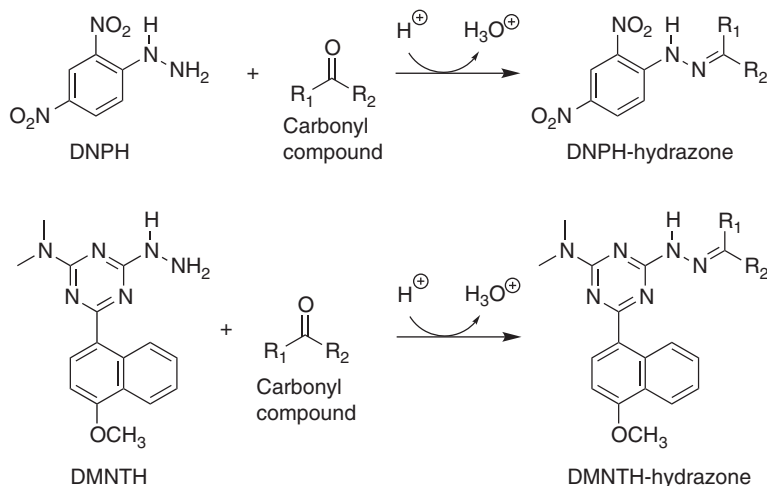


Figure 12.5 Examples of DNPH and DMNTH derivatization reactions for carbonyl compounds to yield hydrazone products.

12.6 Disinfection By-Products (DBPs) in Drinking Water

Drinking water DBPs are formed by the reaction of disinfectants (Cl₂, chloramines, O₃, ClO₂, etc.) with natural organic matter and bromide or iodide in source waters. They can also be formed by the reaction of disinfectants with other organic contaminants. This is an area of increasing research.

In a study of the occurrence of DBPs in 35 water facilities across the United States, THMs (44 µg L⁻¹) were the largest class of DBPs detected, followed by HAAs (21 µg L⁻¹) [23]. Similar results were confirmed by numerous studies including those conducted by Chen and Weisel [21] in New Jersey and Shin *et al.* [52] in Korea. The studies by both Krasner *et al.* [23] and that of a national American survey of 727 water utilities [53] found a median total THM (TTHM) value of 39 µg L⁻¹, while Chen and Weisel [21] and Shin *et al.* [52] found lower levels. Studies in Canada showed a similar pattern [54]. A study in northern England found TTHM levels of on average 50 µg L⁻¹, with a fairly large spread in the mean of the water zones [55].

Chloroform is usually the most prevalent by-product compound formed, although brominated THMs can occur at high levels when waters with high bromide levels are chlorinated (see Table 12.4).

Krasner *et al.* [48] conducted a survey of DBP occurrence at 12 drinking-water treatment plants in the United States. This study found that the ratio of the iodinated THMs to the four regulated THMs was 2% on a median basis. The highest formation of iodinated THMs was at a plant that used only chloramines (i.e., no pre-chlorination). In that plant, five iodinated acids were detected.

Halobenzoquinones are a new class of DBP [65]. The occurrence of 8 halobenzoquinones in 9 drinking water plants in the United States and Canada that use chlorination, chloramination, chlorination with chloramination, and ozonation with chloramination has been reported [66].

Table 12.4 Reported chloroform levels in different media.

Media	Concentration ($\mu\text{g L}^{-1}$)	[Ref.]
Drinking water	9.6–15	[23]
	69	[20]
	33	[21]
	20	[52]
Showering and bathing water	27	[56]
	1000	[57]
	86	[58]
	31	[59]
Showering and bathing air ($\mu\text{g m}^{-3}$)	186	[56]
	0.4	[59]
Swimming pool water	33.7	[60]
	365	[61]
	85	[62]
	3.04–27.8	[63]
	68, 73	[64]
Swimming pool air ($\mu\text{g m}^{-3}$)	169.7	[60]
	87	[62]
	7.78–92.8	[63]

In a DBP-occurrence survey in the United States, for some waters with high total organic carbon and/or high bromide, relatively high levels of the chlorinated furanone 3-chloro-4-(dichloromethyl)-5-hydroxy-2-(5H)-furanone (MX) and its brominated analogs (BMXs) were detected [48].

Several studies have investigated the occurrence of emerging N-DBPs. Besides haloamides, other N-DBPs of interest include NDMA and other nitrosamines, which can form with either chloramination or chlorination (if nitrogen-containing coagulants are used in the treatment). The most extensive occurrence of nitrosamines to date was reported by Boyd *et al.* [67], who used a recently developed LC/ESI-MS/MS method to measure 9 nitrosamines in 38 drinking-water treatment plants in the United States and Canada. NDMA, NDPhA, and NMor were detected, with NDMA being the most common, in finished water from chloramination and chlorination treatment plants and in the distribution system of a plant that used ozone followed by chlorine. The maximum level was found to be 130 ng L^{-1} , and NDPhA was the second-most detected nitrosamine in these drinking waters.

12.7 Disinfection By-Products in Swimming Pools

The water of swimming pools should be of the same quality as drinking water [68]. DBPs have been found not only in drinking water, but also in swimming

pools, which are being recognized as a major source of exposure to DBPs. Health concerns include increased risk of bladder cancer from exposure to indoor pools and increased risk of asthma for indoor and outdoor pools [69].

Weisel and Shepard [70] measured mean chloroform levels of $85 \mu\text{g L}^{-1}$ in the water and $87 \mu\text{g m}^3$ in air in swimming pools. Lindstrom *et al.* [64] reported chloroform levels of 68 and $73 \mu\text{g L}^{-1}$ in the water. Slightly lower levels were measured in both air and water by Cammann and Hubner [63] in Germany. They also measured CHClBr_2 , CHCl_2Br , and bromoform, but these were much lower than the chloroform levels with a maximum of 6.51 in water and $22.4 \mu\text{g m}^3$ for CHCl_2Br in air. In Holland, Aiking *et al.* [71] measured chloroform water concentrations of $18.4 \mu\text{g L}^{-1}$ in indoor pools and $24.0 \mu\text{g L}^{-1}$ in outdoor pools.

The formation of halobenzoquinones in swimming pools has been investigated; for example, 8 halobenzoquinones in 10 swimming pools [65]. In all pools, 2,6-dichlorobenzoquinone was found at concentrations in the range of 19–299 ng L^{-1} , which is as much as 100-fold the levels found previously in drinking water. Kim and Weisel [72] found average dichloroacetic acid (DCAA) levels to be $419 \mu\text{g L}^{-1}$ and average trichloroacetic acid (TCAA) levels to be $420 \mu\text{g L}^{-1}$ in the water of three swimming pools (see Table 12.5).

Aggazotti *et al.* [75, 76], who made a series of studies in Modena (Italy), correlated chloroform concentrations in air and water with the number of swimmers. Further, the chloroform concentration in water was correlated with free and combined chlorine residual and water pH [76], but these were generally only weak to moderate correlations. Another study conducted by Hansen *et al.* [77], investigated the formation of DBPs from particles in swimming-pool filters.

12.8 Changes in Oxidation/Disinfection Strategies

Different disinfection practices have led to different DBP trends. In the United States, there has been an increasing use of alternative disinfectants (O_3 , ClO_2 , and/or UV for primary disinfection; and chloramines for secondary disinfection). In addition, many U.S. utilities have switched from using gaseous chlorine to hypochlorite solutions. In Southern Europe and the United Kingdom, Cl_2 has

Table 12.5 TCAA concentration in different media (water sources).

Medium	Concentration	[Ref.]
Drinking water	4–6 $\mu\text{g L}^{-1}$	[23]
	4.3–15.6 $\mu\text{g L}^{-1}$	[73]
	5.8–56.7 $\mu\text{g L}^{-1}$	[54]
	5.5–10 $\mu\text{g L}^{-1}$	[21]
Swimming pool water	420 $\mu\text{g L}^{-1}$	[72]
Urine	0–30 ng min^{-1}	[74]
	6.35–10.3 ng min^{-1}	[59]
Water	1.94–27.6 ng L^{-1}	[59]

predominantly been used. However, chloramines have started to be used in parts of the United Kingdom. In Central Europe (e.g., Berlin, Zurich, and Vienna), treatment has focused on achieving biostability so that Cl_2 can be eliminated in the distribution system. In Paris, low chlorine levels have been used in the distribution system, where booster chlorination has been used where appropriate. In many Central European countries, O_3 has been used for disinfection and micropollutant (e.g., atrazine) destruction [78].

Bromate has been found in hypochlorite solutions [79]. As a result, NSF International has set a limit on bromate concentrations in commercially prepared hypochlorite solutions. In terms of controlling bromate formation during ozonation, recent research has shown that the use of ClO_2 as a pre-oxidant can reduce bromate formation during subsequent ozonation. ClO_2 satisfied some of the initial oxidant demand of the water, reducing the O_3 dose required to meet treatment goals. However, the ClO_2 by-product chlorite was oxidized to chlorate, an emerging DBP of concern. In other research, chlorine was added to oxidize the bromide and then ammonia was added prior to the ozone contactor to form bromamines [80, 81].

In the “chlorine-ammonia” process, bromate formation was minimized, but other regulated DBPs (e.g., THMs) were produced. Recently, the “chlorine-ammonia” process has been evaluated. This process, especially at pH 7, reduced bromate formation with minimal THM formation.

Two significant changes in disinfection strategies have occurred over the past decade:

- 1) Increased use of chloramines for secondary disinfection in distribution systems in the United States [50].
- 2) Use of UV irradiation for in-plant disinfection.

Chloramines are often applied as a secondary disinfectant in order to minimize THM and HAA formation and to maintain disinfectant residuals in distribution systems. Because chloramines are weak disinfectants, primary disinfection with Cl_2 , ClO_2 , O_3 , or UV is almost always required for surface-water systems. THMs and HAAs still form in the presence of chloramines, but at much slower rates than in the presence of free chlorine. However, dihalogenated HAAs can form in the presence of chloramines. Overall, chloramines decrease THM, HAA, and TOX formation, but tend to increase the percentage of unidentifiable TOX [38]. Additionally, certain nitrogen-containing DBPs, including nitrosamines and cyanogen halides, preferentially form during chloramination [44], some of which may pose more serious potential health issues than non-nitrogen-containing DBPs.

Although the use of O_3 as a primary disinfectant has continued to grow, there has been a significant growth in the use of UV irradiation for primary disinfection, due mainly to the need for some systems to inactivate *Cryptosporidium* [10]. At UV dosages used for microbial inactivation, there has typically been no evidence that UV irradiation affects DBP formation [11]. The order of chlorine and UV application can affect THM production [82]. However, medium-pressure UV can increase the formation of chloropicrin and may also increase the formation of other HNMs of health concern [83]. In addition, it is possible to form nitrite with medium pressure UV. With a significant percentage of DBPs still unaccounted

for in drinking water, increased public concern over the potential carcinogenicity and reproductive/developmental toxicity to humans, innovative ideas and further work are needed to ensure that the public is adequately protected [4].

12.9 Toxicological Studies on DBPs

While pathogenic organisms provide the primary human-health risk from drinking water, chemical DBPs also pose an unintended health hazard.

Although the microbiological quality of drinking water cannot be compromised, there is a need to better understand the chemistry, toxicology, and epidemiology of chemical disinfectants and their associated DBPs in order to specify the health risks (microbial and chemical) associated with drinking water and to seek a balance between potential microbial and chemical hazards. It is possible to decrease the chemical risk due to DBPs without compromising microbiological quality.

Humans are exposed to DBPs through drinking water and oral, dermal, and inhalational contact with chlorinated water [84]. In populations who take hot showers or baths, inhalation and dermal absorption in the shower accounts for more exposure to THMs than drinking water [85].

Because there has been such a large number of DBPs (> 500) reported over the past 40 years, it has been difficult to have focus on DBP toxicological work beyond those regulated and commonly measured, which include THMs, HAAs, bromate, chlorite, chloropicrin, chloral hydrate, and dichloroacetonitrile. Toxicologically important DBPs include brominated, iodinated, and nitrogen-containing DBPs (N-DBPs). Brominated DBPs are generally more carcinogenic than their chlorinated analogs, and results have indicated that iodinated compounds are more toxic than their brominated analogs [49]. Brominated and iodinated DBPs form as a result of the reaction of the disinfectant (such as chlorine or chloramines) with natural bromide or iodide present in source waters. The DBPs of most interest are THMs, HAAs, bromate, and chlorite.

Health research has focused on THMs, a volatile group of compounds that comprises chloroform, CHCl_2Br , CHClBr_2 , and bromoform, which are classified as possible human carcinogens by the WHO. These occur in the highest quantities, and are routinely measured throughout water supplies. According to the International Agency for Research on Cancer (IARC) monographs, chemical agents are classified into five groups, THMs being in groups 2B and 3:

Group 1: Carcinogenic to humans.

Group 2A: Probably carcinogenic to humans.

Group 2B: Possibly carcinogenic to humans (e.g., chloroform, CHCl_2Br).

Group 3: Not classifiable as to its carcinogenicity to humans (e.g., bromoform and CHClBr_2).

Group 4: Probably not carcinogenic to humans.

Epidemiological studies have focused on the possible association between exposure to these by-products and the incidence of human cancer, particularly

pancreatic cancer [86] and rectal cancer [87], and adverse reproductive outcomes [88].

Plewa *et al.* [43, 83] have conducted genotoxicity and cytotoxicity studies of brominated and chlorinated DBPs using mammalian cell assays. Specifically, in a study of brominated *versus* chlorinated haloacetic acids, the brominated HAAs were found to be more cytotoxic and genotoxic than their chlorinated analogs [43]. The cytotoxicity rank order was found to be bromoacetic acid \gg dibromoacetic acid $>$ chloroacetic acid $>$ tribromoacetic acid $>$ dichloroacetic acid $>$ trichloroacetic acid. The genotoxicity rank order was bromoacetic acid \gg chloroacetic acid $>$ dibromoacetic acid $>$ tribromoacetic acid; dichloroacetic acid and trichloroacetic acid were not found to be genotoxic in this assay. A similar comparison has also been made for a series of brominated *versus* chlorinated nitromethanes [83].

However, there is concern about the chemical DBPs formed, because some laboratory studies have linked these to incidence of cancer in animals [89], and many others still remain to be studied. There are also concerns about possible reproductive and developmental effects from exposure to DBPs [90–94]. Iodo-DBPs are among the most genotoxic DBPs measured to date, and iodoacetic acid was recently shown to be tumorigenic. Iodoacetic acid was recently discovered as a chloramination DBP and is the most genotoxic of all DBPs studied to date [3]. As such, research is increasing on this important DBP class. Pan and Zhang [95] reported a new method to measure total organic iodine, using UPLC/ESI-MS for off-line iodide separation and detection.

12.10 Regulations/Guidelines of DBPs in Drinking Water

Disinfectants are powerful oxidants that oxidize the organic matter and bromide naturally present in most source waters (rivers, lakes, and many groundwaters) forming DBPs. The most common disinfectants in use are Cl_2 , O_3 , ClO_2 , and NH_2Cl and each produces its own suite of chemical DBPs in finished drinking water [24].

Most developed nations have created regulations or guidelines to control DBPs to minimize consumers' exposure to hazardous compounds, while, at the same time, maintaining adequate disinfection and control of targeted pathogens.

In 1976, the USEPA published the results of a national survey that showed that chloroform and the other THMs were ubiquitous in chlorinated drinking water. In addition, in 1976, the U.S. National Cancer Institute published results linking chloroform to cancer in laboratory animals. As a result, an important public-health issue was born.

In 1979, the USEPA issued a regulation to control THMs at $100\text{ }\mu\text{g L}^{-1}$ (ppb) in finished drinking water. In 1998, the Stage 1 Disinfectants/Disinfection By-products (D/DBP) Rule was promulgated, which lowered permissible levels of THMs to $80\text{ }\mu\text{g L}^{-1}$ and regulated five HAAs, bromate, and chlorite for the first time.

Table 12.6 Total THM regulatory limits in different countries and regions.^{a)}

Country and region	Limit ($\mu\text{g L}^{-1}$)	Country and region	Limit ($\mu\text{g L}^{-1}$)
Austria	30	Luxembourg	50
Belgium	30	Norway	100
China	100	Spain	100
Czech Republic	100	Sweden	50
Germany	50	Scotland	100
Ireland	100	Taiwan	80
Italy	30	U.K.	100
Japan	100	U.S.	80

a) Data taken from Ref. [78].

A conducted U.S. Nationwide DBP Occurrence Study has helped to provide focus with quantitative occurrence data for new DBPs that had little or no previous occurrence information. Because it is not feasible to conduct an occurrence study on all DBPs reported in the literature, this entire group of DBPs (> 500) was prioritized for the study according to predicted adverse health effects (cancer) by a multidisciplinary group of experts, including toxicologists, structure-activity specialists, and chemists [96].

There has been an active regulatory process for DBPs around the world within the past 10 years. In the United States, Stage 2 of the D/DBP Rule was published in 2006 [97], requiring water utilities to comply with maximum contaminant levels (MCLs) of $80 \mu\text{g L}^{-1}$ of THMs and $60 \mu\text{g L}^{-1}$ of five haloacetic acids (HAA5) at each individual monitoring location in a distribution system, which will commence in the next six years. As part of this Rule, the MCL for bromate was kept at $10 \mu\text{g L}^{-1}$. However, the bromate MCL will be reexamined as part of the six-year review of the Rule. Moreover, there is an MCL for chlorite (but not chlorate) at 1.0 mg L^{-1} [98].

The WHO has guideline values for DBPs in drinking water. These are $10 \mu\text{g L}^{-1}$ for bromate, $60 \mu\text{g L}^{-1}$ for bromodichloromethane, $100 \mu\text{g L}^{-1}$ for bromoform, $700 \mu\text{g L}^{-1}$ for chlorate, $700 \mu\text{g L}^{-1}$ for chlorite, $300 \mu\text{g L}^{-1}$ for chloroform, $70 \mu\text{g L}^{-1}$ for ClCN, $70 \mu\text{g L}^{-1}$ for dibromoacetonitrile, $100 \mu\text{g L}^{-1}$ for dibromochloromethane, $50 \mu\text{g L}^{-1}$ for dichloroacetate, $20 \mu\text{g L}^{-1}$ for dichloroacetonitrile, $20 \mu\text{g L}^{-1}$ for monochloroacetate, $200 \mu\text{g L}^{-1}$ for trichloroacetate, and $200 \mu\text{g L}^{-1}$ for 2,4,6-trichlorophenol. In addition, for THMs, the sum of the ratio of the concentration of each to its respective guideline value should not exceed 1.

In the EU, the European Council adopted Directive 98/83/EC [99], establishing standards for the member states. Total THMs and bromate were selected as representative by-products of chlorination and ozonation, respectively. The standard for THMs was set at $150 \mu\text{g L}^{-1}$ by 2003 and $100 \mu\text{g L}^{-1}$ by 2008. The bromate standard was $10 \mu\text{g L}^{-1}$, with an interim value of $25 \mu\text{g L}^{-1}$. Table 12.6 shows regulatory limits in different countries.

Five nitrosamines (NDMA, *N*-nitroso-di-*n*-propylamine (NDPA), *N*-nitrosodiethylamine (NDEA), *N*-nitrosodiphenylamine, and *N*-nitrosopyrrolidine) as well as acetaldehyde and formaldehyde (which is a DBP from treatment with O₃, ClO₂, or Cl₂), are currently listed on the USEPA CCL-4.⁶

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13

Other Contaminants of Emerging Concern

13.1 Introduction

Recent advances in analytical techniques and instrumentation have permitted the identification of others pollutants of concern that have emerged, such as NMs, microplastics (MPs), and algal toxins. Nanotechnology is recognized as one of the most promising new technologies of the twenty-first century. Widespread application of nanotechnology in a variety of industrial sectors has spawned new wastes, which could potentially impact human health and ecology. Two major sources that contribute to the environmental occurrence of NP include the myriad of anthropogenic activities and natural events. Engineered nanomaterials (ENMs) are used in practically every aspect of human endeavors including but not limited to, industrial or agricultural applications, biomedicine, and PCs and PCPs.

Plastic poses a great threat to the health of the world's seas and oceans [1], plastic pollution being one of the main aspects of the occurrence of MPs (particles smaller than 5 mm) in the aquatic ecosystem. MPs are ubiquitous in various environmental compartments: the water column, sediment, and biota.

Algal toxins are extremely potent neurotoxins or hepatotoxins that are produced from dinoflagellates, diatoms, or cyanobacteria (blue-green algae). Concerns were originally limited to poisoning of shellfish, large fish kills, deaths of livestock and wildlife, and illness in swimmers. However, recent discoveries of cyanobacterial toxins in finished drinking water have also extended these concerns to adverse human effects through drinking-water ingestion.

Generally, metals are found in the environment in amounts that do not cause health threats. These contaminants can also have anthropogenic origins, which often cause the release of a large amount of naturally occurring minerals into the environment. Moreover, it is not the mere presence of a contaminant that makes it toxic, it is its concentration.

13.2 Nanotechnology as a Pollution Source

Nanotechnology promises new materials for industrial applications by having new or enhanced physicochemical properties that differ from those of their

micron-sized counterparts. In the near future, NMs are projected to be used in areas such as chemotherapy, drug delivery, and the labeling of food pathogens (nanobarcodes).

NMs are either natural or synthetic structures in the nanometer scale and can have unique properties, including high strength, thermal stability, low permeability, and high conductivity. These materials comprise a diverse class of small-scale substances, for example, NPs at least two dimensions in the 1–100 nm size range [2]. NMs can be categorized into three types according to their source: natural, incidental, and engineered. The chemical structures of NMs are highly varied, including those of fullerenes, nanotubes, quantum dots, metal oxanes, TiO_2 and CeO_2 NPs, nanosilver, nanogold, and zerovalent iron NPs. Meanwhile, ENMs are classified into five major groups:

- Fullerenes (a.k.a. buckyballs)
- Nanotubes
- Quantum dots
- Nanopowders (metal oxides)
- Natural particles (e.g. soot).

CNTs are a group of nanoparticles that are considered a novel material with growing commercial application due to their unique properties. Discovered in the early 1990s, CNTs are tubular, graphite sheets consisting of sp^2 carbon bonds typically with diameters of 1.4 nm and lengths in microns [3]. The large surface-area-to-volume ratio, tensile strength, and electrical properties make CNTs ideal components of composites, sensors, probes, and energy-storage devices, such as fuel cells. In the United States alone, \$1.5 billion was invested in nanotechnology in 2008 [4].

SWCNTs, formed from single-atom thick sheets of carbon wound into nanometer scale tubes [5], display a number of remarkable properties ranging from superior tensile strength, thermal and electrical conductivity, and relative ease of chemical modification (see Figure 13.1) [6]. These properties make CNTs promising components in next-generation thermo polymers, electronics, and drug-delivery systems [7, 8]. As a result of their wide range of uses and the rapidly advancing production methods, CNTs are increasingly prevalent in manufactured products. Despite the increase in CNT production, very little is known about the eventual fate of CNTs once introduced into the environment through accidental release, by dispersal in landfills, and as a part of biosolid waste for land application [9, 10].

Nano- TiO_2 is the most widely produced of all NMs and is used in textiles as a UV filter and as a pigment. More than 1000 consumer products that contain NMs are on the market today [11].

13.2.1 Detection of NMs

The detection, extraction, and analysis of NMs are challenging due to their small size, unique structure, physicochemical characteristics, surface coatings, and interactions in the environment, including agglomeration and sequestration.

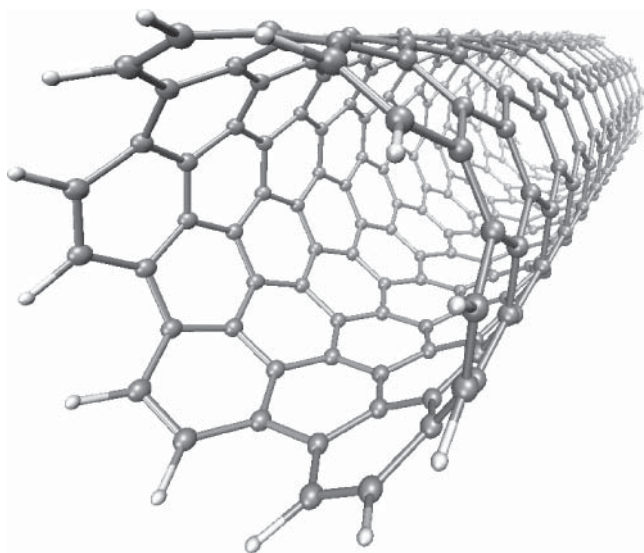


Figure 13.1 Scheme of the structure of a single-walled carbon nanotube (SWCNT).

The analysis of NMs in environmental samples often requires the use of multiple technologies in tandem. This can include the use of size-separation technologies combined with particle-counting systems, morphological analysis, and/or chemical-analysis technologies.

MS techniques used for measuring NMs include inductively coupled plasma (ICP)MS and single-particle ICPMS (for metals containing NMs), and ESI- and APPI-MS/MS for fullerenes.

Most methods use techniques other than MS, such as transmission electron microscopy (TEM), scanning electron microscopy (SEM), atomic force microscopy (AFM), flow field-flow fractionation (FIFFF), dynamic light scattering (DLS), quartz-crystal microbalance, energy dispersive X-ray spectroscopy (EDS), X-ray photoelectron spectroscopy, static light scattering (SLS), particle electrophoresis, LC/UV, Raman spectroscopy, and NMR spectroscopy.

Aerosol fractionation technologies (differential mobility analyzers and scanning mobility particle sizers) use the mobility properties of charged NMs in an electrical field to determine size fractions for subsequent analysis. Multi-stage impactor samplers separate NM fractions based upon the aerodynamic mobility properties of the NMs [12]. Aerosol mass spectrometer provides chemical analysis of NMs suspended in gases and liquids by vapourizing them and analyzing the resulting ions in a mass spectrometer [13]. Currently available instruments can detect NMs as small as 3 nm [14]. Moreover, size-exclusion chromatography, ultrafiltration, and field-flow fractionation can be used for size fractionation and collection of NM fractions in liquid media.

Chen and Ding [15] reported an LC/APPI-MS/MS method using ultrasound-assisted DLLME for measuring fullerenes in aqueous samples. CNTs were the focus of other methods, including the most sensitive and selective technique available to date for SWCNTs developed by Schierz *et al.* [16].

Other analytical techniques include X-ray diffraction to measure the crystalline phase and X-ray photoelectron spectroscopy to determine the surface chemical composition and functionality of NMs.

13.2.2 NMs in the Environment

Naturally occurring NPs have existed in the environment for millions of years and it is obvious that humans to some extent must have evolved and adapted to live in their presence [17]. Not much is known about the impact on human health or ecology from exposure to ENMs introduced in the environment due to anthropogenic activities.

ENMs designed with very specific properties, are intentionally produced through certain physicochemical processes, such as self-assembly (from atoms and molecules) or milling (from their macro-scale counterparts), and may be released into the environment primarily through industrial and environmental applications or improper handling of NMs.

ENMs are used simply because they offer easy ways to manipulate their physicochemical properties [18]. Various sources contribute to the environmental occurrence of ENMs ranging from waste products from industrial processes to accidental releases. These include combustion processes, industrial emissions, atmospheric deposition, sorption, and transport to aquatic systems [19]. The following routes contribute to the entry of ENMs in the environment (soil and water):

- Atmospheric transformation
- Combustion
- Buried solid waste
- Waste discharge from industrial emissions
- Automobile traffic
- Laundry
- Food water
- PCs and PCPs
- Consumer goods.

ENM resulting from various applications, including cosmetics and textiles, will be discharged to wastewater. Urban wastewater systems, including sewers, WWTPs, and sludge-incineration plants have therefore been identified as critical “facilities,” controlling the transfer of ENM to the (aquatic) environment.

NMs in solid wastes, wastewater effluents, direct discharges, or accidental spillages may be transported to aquatic systems by wind or rainwater runoff [20]. The fate of NPs and their transport in the environment depend largely on material properties such as surface chemistry, particle size, and biological and abiotic processes in environmental media. Depending on these properties, NPs may remain in suspension as individual particles, aggregate to form larger-sized NMs, dissolve, or react with natural materials. Because of their small size and slower rate of gravitational settling, some NMs may remain suspended in air and

water during longer periods and may be readily transported over much greater distances than larger particles of the same material.¹

As with the vast majority of industrial products, the environmental fate of CNTs depends partially on degradation by microorganisms found in soils, sediments, and landfills [20]. Commercially produced CNTs have lengths on par, or much larger than, many biological cells with aspect ratios of 1 up to 10^6 , making intracellular degradation unlikely. Studies continue to be published on the environmental fate of NMs. For example, Alpatova *et al.* [21] reported the first evidence that nC₆₀ can form chlorinated disinfection by-products.

With respect to the interaction of engineered NPs with soil particles, there are relatively few studies [22], and those that exist point to a different behavior from that of contaminants not composed of distinct substances and warn that new models and paradigms will be needed to be developed for NPs in the soil environment.

13.2.3 Toxicity of NMs

The toxicity of most nanotechnology products has not been determined. The majority of studies of NMs are carried out in “clean” systems and not in real environmental systems. Moreover, currently no specific federal standards regulate NMs based solely on their size. Potential mechanisms of aquatic toxicity from the particles themselves are the following:

- Ingestion
- Physical disruption
- Gill irritation.

Human exposure to NMs may occur through ingestion, inhalation, injection, and dermal exposure depending on the source and activities of the person. In the workplace, inhalation is a widely prevalent route of human exposure [23]. The small size, solubility, and large surface area of NMs may enable them to translocate from their deposition site (typically in the lungs) and interact with biological systems. Circulation time increases drastically when the NMs are water soluble. With smaller NM sizes, the likelihood of greater pulmonary deposition and potential toxicity exists [13].

The health effects of NMs are variable according to their characteristics. Depending on their charge and particle size, NMs can induce different levels of cell injury and oxidative stress. In addition, particle coatings, size, charge, surface treatments, and surface excitation by UV radiation can modify surface properties and thus the aggregation and biological effects of NMs [24].

Some NPs may generate reactive oxygen species, which can lead to membrane damage, including increases in membrane permeability and fluidity. Cells may become more susceptible to osmotic stress or impaired nutrient uptake [20].

1 EPA. 2009. Office of Research and Development. Final Nanomaterial Research Strategy (NRS). <http://www.epa.gov/ord/index.htm>.

Studies have shown that NMs, due to their small size, have the potential to pass through both the blood–brain barrier and the placenta. For example, a recent study showed that nano-anatase TiO_2 may pass the blood–brain barrier of mice when injected with high doses [25]. Ingestion exposure may occur from consuming NMs contained in drinking water or food (e.g., fish) [26].

Metal-containing NMs may cause toxicity to cells by releasing harmful trace elements or chemical ions. For example, silver NMs may release silver ions that can interact with proteins and inactivate vital enzymes. Research on the impacts of carbon NMs on microorganisms has been largely focused on the impact of NMs on bacterial monocultures where both CNT and fullerenes have demonstrated antimicrobial properties [27, 28].

13.3 Microplastics (MPs)

Because plastic products are made of hydrocarbons, they can be burned. However, certain chlorine-rich plastic products, such as PVC, form dioxins when incinerated. Because oil-based plastics are not biodegradable, most man-made plastic that is not burned still exists today. Plastic waste is created in staggering numbers: Some 299 million t of plastics were produced in 2013.² Plastic goods most often end up in municipal dumpsites and landfills. Plastic is an inert material and therefore not toxic, but the problem arises from the fact that it does not degrade. Plastic litter comprises most worldwide marine litter, with fishing and merchant and recreational ships as the major sources of plastic litter [29]. Plastic litter is harmful to marine organisms in several ways. Plastic products are known to eventually break down into smaller and smaller pieces (nanoparticles) until they are small enough to enter the cells of living organisms. Because the amount of discarded plastic is so substantial, nanoplastic particles pose an emerging environmental concern. The health hazards of nanoplastics are not thoroughly understood, but polystyrene particles up to 240 nm in diameter have been proven to be transportable through placental cells [30].

Plastics clearly offer remarkable societal benefits [31], but their durability, unsustainable use, and inappropriate waste management causes an extensive accumulation of plastics in natural habitats [32]. It is commonly reported that plastic poses a great threat to the health of the world's seas and oceans [1]. In the marine environment, plastics of various size classes and origins are ubiquitous and affect numerous species that become entangled in or ingest plastics [33].

One major aspect of plastic pollution is the occurrence of MPs (plastic particles smaller than 5 mm) in the aquatic ecosystem. MPs can be the products of degradation of larger plastic items into smaller fragments, or may originate from cosmetics and synthetic fabrics [34, 35].

Environmental plastics are a very heterogeneous group of litter that can be characterized by various descriptors and there is no common classification system. The European MSFD Working Group on Good Environmental Status (WG-GES) provided a “Monitoring Guidance for Marine Litter in European

² <http://www.worldwatch.org>.

Seas,” [36] which represents a key step toward a standardized sampling and monitoring of marine MPs. Thus, environmental MPs can be classified into the following categories [37]:

Size: The WG-GES defines size classes for plastic litter as follows: macroplastics (>25 mm), mesoplastics (5–25 mm), large MPs (1–5 mm), and small MPs (20 μm to 1 mm). Accordingly, items smaller than 20 μm will be classified as nanoplastics.

Origin: MPs can also be categorized according to their origin: primary MPs are produced as such, for instance as resin pellets (raw materials for plastic products) or as additives for PCPs (e.g. shower gels and peelings), while secondary MPs are degradation products of larger plastic items, which are broken down by UV radiation and physical abrasion into smaller fragments.

Polymers: The polymer type of environmental MPs can be determined by Fourier transformed infrared spectroscopy (FT-IR) or Raman spectroscopy. In accordance with global production rates, high- and low-density polyethylene (HD/LD-PE), PET, polypropylene (PP), polystyrene (PS), and PVC are the most common polymers found in the environment. In addition, polyamide fibers (nylon) from fishing gear are frequent.

Shape: The shape can be described according to the main categories: fragments (rounded, angular), pellets (cylinders, disks, spherules), filaments (fibres), and granules.

MPs, ubiquitous in various environmental compartments, have a worldwide distribution [38] and have been detected in all levels of the marine environment [1, 39, 40]. Their widespread occurrence implies a potential to influence marine ecosystems worldwide. For example, MP ingestion has been demonstrated in a wide array of marine organisms [41, 42].

MP extraction was based on the principle of wet digestion of tissues using acid. Two acid-digestion methods are usually performed: the “acid mix method” uses a combination of nitric acid and perchloric acid according to the protocol of De Witte *et al.* [43] and the nitric acid method used only nitric acid according to Claessens *et al.* [44].

MPs can have physicochemical and biological impacts on organisms that ingest them directly, but potentially also on organisms that ingest them indirectly through the consumption of contaminated prey [41, 45, 46].

MPs are of special concern because their bioaccumulation potential increases with decreasing size. MPs may be ingested by various organisms ranging from plankton and fish to birds and even mammals, and may accumulate throughout the aquatic food web [41]. In addition, plastics contain a multitude of chemical additives [47] and adsorb organic contaminants from the surrounding media [48]. Since these compounds can transfer to organisms upon ingestion, MP act as vectors for other organic pollutants [49] and are, therefore, a source of wildlife exposure to these chemicals (see Figure 13.2) [50, 51]. Studies have found the occurrence of MPs in aquatic organisms [52].

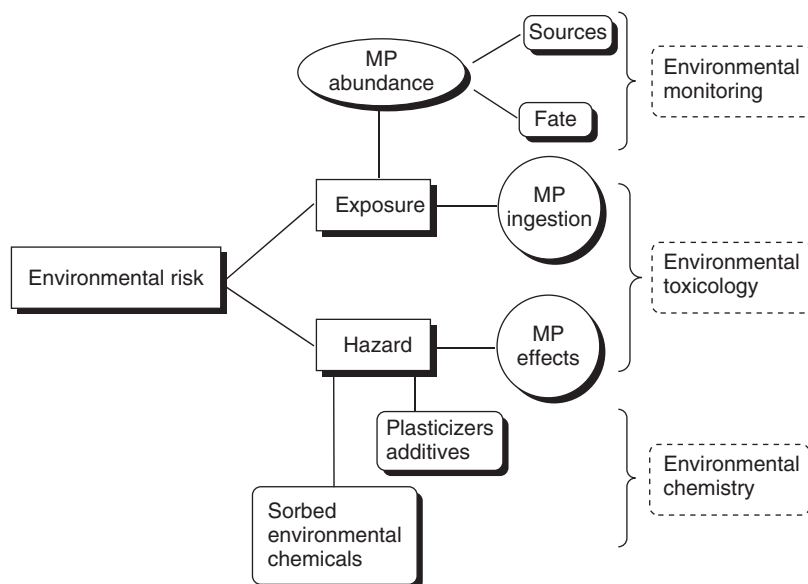


Figure 13.2 Environmental risk of MPs in freshwater.

13.4 Toxic Elements and Elemental Species

In 2010, the WHO listed four elements (As, Pb, Hg, and Cd) on their prioritized list of the top 10 chemicals of major public-health concern.³ These elements, and other elements with toxic properties, are often called by a well-known term “heavy metals,” although the term is not accepted in the scientific community [53]. An alternative term is “toxic elements.” Although this term neither has general scientific consensus nor an exact definition, it seems to be more broadly accepted and is therefore used here [54].

Contamination with toxic elements is a worldwide recognized public-health hazard because these pollutants are widespread in the environment from either natural (e.g., mineral weathering, volcanic activities) or anthropogenic sources (e.g., agricultural practices, industrial release) [55].

Some elements have nutritional functions essential to life (e.g., selenium, iodine, and zinc) and for maintenance of a number of functions in the human body, and their deficiency results in serious symptoms. The best examples are anemia for lack of iron, diabetes for lack of chromium, and growth problems for lack of nickel. By contrast, other elements, for example, lead, cadmium, mercury, arsenic, and molybdenum, have no nutritional properties and intake of these elements have been shown to induce serious toxic effects. Thus, the daily requirement of Co, the central atom of vitamin B12 (cobalamin), which is necessary in the formation of erythrocytes, is about 0.1 μg , whereas 25–30 mg d^{-1} induce symptoms of poisoning in the gastrointestinal tract, heart, and kidney.

³ World Health Organization (WHO), 2010. Ten Chemicals of Major Public Health Concern. http://www.who.int/ipcs/assessment/public_health/chemicals_phc/.

Table 13.1 Toxic elements emissions from different industrial sectors.^{a)}

Industrial sector	Heavy metals							
	Cd	Cr	Cu	Hg	Pb	Ni	Sn	Zn
Paper industry	–	✓	✓	✓	✓	✓	–	✓
Petrochemistry	✓	✓	–	✓	✓	–	✓	✓
Production of chlorine	✓	✓	–	✓	✓	–	✓	✓
Fertilizer industry	✓	✓	✓	✓	✓	✓	–	✓
Petroleum refineries	✓	✓	✓	–	✓	✓	–	✓
Steelworks and ironworks	✓	✓	✓	✓	✓	✓	✓	✓
Non-ferrous metals	–	✓	✓	✓	✓	–	–	✓
Motor vehicles, air craft	✓	✓	✓	✓	✓	–	✓	✓
Glass, cement, ceramics	–	✓	–	–	–	–	–	–
Textile/leather	–	✓	–	–	–	–	–	–
Steam power plant	–	✓	–	–	–	–	–	✓

a) Data taken from Ref. [57, 58].

Elements may change their chemical form in the environment, but they cannot be degraded over time. This means that they are environmentally persistent and may bioaccumulate in plants and animals [56]. Table 13.1 lists certain branches of industries that emit toxic elements.

Chronic exposure to toxic elements may cause several adverse effects to human health, even at relatively low quantities. Toxicologically, the chemical form (i.e., the elemental speciation) in which the element is ingested may play a significant role. For example, methylmercury is considered to be much more toxic than inorganic Hg compounds, while inorganic As is considered to be more toxic than the organic species of As [59].

Toxic elements may be in the form of fine dust particles to end up in the atmosphere, where they are precipitated in water and soil. In water, heavy metals are quickly diluted and precipitated as sparingly soluble carbonates, sulfates, sulfides, or at the bottom of the water surface. When the adsorption capacity of sediments is exhausted, the concentration of metal ions increases in the water. Circulation of heavy metals in nature is highly dependent on changes that are subject to these metals. Toxicity of heavy metal in particular increases in the chelating process and creation of sulfide with biologically active substances, particularly enzymes. This procedure is called biomethylation. A special toxicity is exhibited by organometallic compounds of Hg, Pb, Cr, and Se.

Toxic elements can also occur in food, either because of their natural presence in the environment or from contamination during food production, processing, and storage. Fish and shellfish have been identified as the food items typically showing the highest concentrations of a number of toxic elements [60, 61]. The maximum levels of certain elements (Pb, Cd, and total Hg) in certain types of seafood are subject to the European Commission regulation 1831/2003 [62]; and Amending Regulations 609/2008 [63], 420/2011 [64], and 488/2014 [65]. For

other toxic elements, no maximum levels have been established in the European legislation, partly due to a lack of information about their presence in seafood.

13.4.1 Arsenic (As)

The primary use of metallic As is in alloys of Pb (e.g., in car batteries and ammunition). As is a common n-type dopant in semiconductor electronic devices, and the optoelectronic compound gallium arsenide is the second most commonly used semiconductor after doped silicon. Arsenic and its compounds, especially trioxide, are used in the production of pesticides, treated wood products, herbicides, and insecticides.

Trace quantities of As are an essential dietary element in many species, including humans. However, As poisoning occurs in multicellular life when quantities become larger than tolerable. Arsenic contamination of groundwater is a problem that affects millions of people across the world.

Arsenic constitutes about 1.5 ppm (0.00015%) of the Earth's crust. Typical background concentrations are as follows: Air $<3 \text{ ng m}^{-3}$; soil $<100 \text{ mg kg}^{-1}$; freshwater $<10 \text{ } \mu\text{g L}^{-1}$; seawater $<1.5 \text{ } \mu\text{g L}^{-1}$ [66]. In 2014, China was the top producer of white arsenic with almost 70% world share, followed by Morocco, Russia, and Belgium [67].

Arsenic's toxicity comes from the affinity of As(III) oxides for thiols. Arsenic disrupts ATP production through several mechanisms. In the United States, since 2006, the maximum concentration in drinking water allowed by the EPA is 10 ppb and the FDA set the same standard in 2005 for bottled water.

The concentrations of total As in marine species vary widely depending on factors such as species type, sampling location, and feeding regime. The highest values for total As are typically observed in species of shellfish reaching values up to $50 \text{ mg kg}^{-1} \text{ ww}$, whereas in fish lower levels are usually reported [68].

13.4.2 Cadmium (Cd)

Cadmium was long used as a corrosion-resistant plating on steel, and Cd compounds are used as red, orange, and yellow pigments, to color glass, and to stabilize plastic. However, Cd use is generally decreasing because of its toxicity. This metal has no known biological function in higher organisms.

Typical background concentrations in other environmental media are atmosphere $<5 \text{ ng m}^{-3}$; soil $<2 \text{ mg kg}^{-1}$; vegetation $<0.5 \text{ mg kg}^{-1}$; freshwater $<1 \text{ } \mu\text{g L}^{-1}$; seawater $<50 \text{ ng L}^{-1}$; and sediment $<2 \text{ mg kg}^{-1}$ [66].

Cadmium is a common impurity in Zn ores, and it is most often isolated during the production of Zn. Cd is a common component of electric batteries, pigments, coatings, and electroplating. The biogeochemistry of Cd and its release to the environment has been the subject of review, as has the speciation of Cd in the environment [69, 70]. The bioinorganic aspects of Cd toxicity have also been reviewed [71].

Environmental concentrations can exceed adverse-effect thresholds in cadmium-polluted ecosystems and pollutant Cd can accumulate in invertebrates, earthworms, seabirds, marine mammals, plants, and some algal species;

effects in animals include kidney disorders, impairment of enzymes, disruption of calcium metabolism, and changes in cell-membrane permeability.

Because of the adverse effects of Cd on the environment and human health, the supply and use of Cd is restricted in Europe under the REACH Regulation.⁴ The EFSA Panel on Contaminants in the Food Chain specifies that $2.5 \mu\text{g kg}^{-1} \text{ bw}$ is a tolerable weekly intake for humans [72]. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has declared $7 \mu\text{g kg}^{-1} \text{ bw}$ to be the provisional tolerable weekly intake level [73].

The observed concentration range for Cd is very wide, depending on the species and tissues studied as well as the sampling location. Since Cd target organs are the viscera, the highest values are typically detected in the liver of some fish [74] and the hepatopancreas of crustaceans, reaching values of up to 30.0 mg kg^{-1} [75]. For muscle tissue, in most species the maximum level of EU legislation (1.0 mg kg^{-1}) is not exceeded [65].

13.4.3 Lead (Pb)

Having no biological role, Pb is considered a highly poisonous metal (whether inhaled or swallowed), affecting almost every organ and system in the body. The component limit of Pb ($1.0 \mu\text{g g}^{-1}$) is a test benchmark for pharmaceuticals, representing the maximum daily intake an individual should have. Even at this level, prolonged intake can be hazardous to human beings. Exposure to Pb and Pb chemicals occurs primarily through ingestion. Pb is a neurotoxin that accumulates in soft tissues and bones, damaging the nervous system and causing brain disorders. Excessive Pb also causes blood disorders in mammals.

The extraction, production, use, and disposal of Pb and its products have caused significant contamination of the Earth's soils and waters, posing a hazard to living organisms because of its toxicity. Atmospheric emissions of Pb were at their peak during the Industrial Revolution and the period of leaded petrol in the second half of the twentieth century; although these are past periods, high concentrations of Pb persist in soils and sediments. Meanwhile, industrial emissions continue in many parts of the world.

Pb accumulates in soil, especially in soil with high organic contents, where it remains for hundreds and thousands of years. According to the USEPA, Pb from soils may take the place of other metals within organic matter, particularly plants. In plants, Pb accumulates on the surface, thus covering the plant from the incoming CO_2 , reducing the rate of photosynthesis, which prevents the growth of the plant or kills it. Contamination of soils and plants, in turn, affects microorganisms and animals. Sources of contamination of the environment with Pb are thus being limited. Generally, Pb values are below the legal maximum levels for most types of seafood species (fish, crustaceans, and molluscs). The values found for muscle tissues are between "not detected" and $0.55 \text{ mg kg}^{-1} \text{ ww}$ [55, 56, 76–78]. The fact that the recent reported values are lower than those reported during 1950–1980 indicates that the contamination sources have declined over recent decades, largely due to the ban of the use of Pb additives in gasoline.

4 EUR-Lex. <http://eur-lex.europa.eu>.

13.4.4 Mercury (Hg)

Hg occurs in deposits throughout the world mostly as cinnabar (mercuric sulfide). Hg is used primarily in the manufacture of industrial chemicals or for electrical and electronic applications. It is used in some thermometers, especially ones that are used to measure high temperatures. A still increasing amount is used as gaseous mercury in fluorescent lamps, while most of the other applications are slowly phased out due to health and safety regulations, in some applications being replaced with less toxic but considerably more expensive Galinstan alloy [79]. Hg remains in use in scientific research applications and in amalgam for dental restoration in some locales.

Hg and most of its compounds are extremely toxic. Hg can be absorbed through the skin and mucus membranes and Hg vapors can be inhaled. The most toxic forms of Hg are its organic compounds, such as dimethylmercury and methylmercury. Hg can cause both chronic and acute poisoning. Hg poisoning can result from exposure to water-soluble forms of Hg (such as mercuric chloride or methylmercury), by inhalation of Hg vapor, or by ingesting any form of Hg.

Natural sources, such as volcanoes, are responsible for approximately half of atmospheric Hg emissions. Human-generated percentages are depicted in Figure 13.3 [80].

Hg also enters the environment through the improper disposal of certain products, such as auto parts, batteries, fluorescent bulbs, medical products, thermometers, and thermostats. Due to health concerns, toward toxic use reduction, efforts are being taken to cut back or eliminate Hg from such products. For

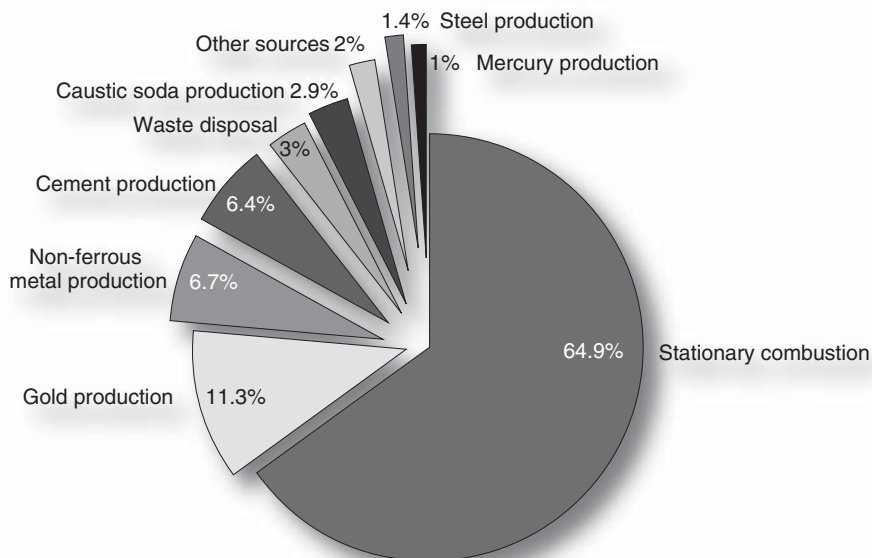


Figure 13.3 Human sources of atmospheric Hg production. Data taken from Ref. [80]

example, the amount of Hg sold in thermostats in the United States decreased from 14.5 t in 2004 to 3.9 t in 2007.⁵

Atmospheric Hg contamination in outdoor urban air was measured at 0.01–0.02 $\mu\text{g m}^{-3}$. A 2001 study measured mercury levels at 12 indoor sites chosen to represent a cross-section of building types, locations, and ages in the New York area. This study found Hg concentrations significantly elevated over outdoor concentrations, at a range of 0.0065–0.523 $\mu\text{g m}^{-3}$, with an average of 0.069 $\mu\text{g m}^{-3}$.⁶

Hg is one of the most analyzed contaminants worldwide. Given the potential of Hg to bioaccumulate and biomagnify in marine food webs, its concentration varies greatly from species to species and also depends on the contamination of the catching area. Thus, Hg levels in fish can range from “not detected” to values of 20 mg kg^{-1} ww [81–84]. The highest values are typically found in carnivorous and predatory species [81, 85–87]. Several studies indicate that the predominant form of Hg in fish is the most toxic form, methylmercury [55, 88–90].

The JECFA establishing the provisional tolerable weekly intakes of 1.6 $\mu\text{g kg}^{-1}$ bw for methylmercury and of 4 $\mu\text{g kg}^{-1}$ bw for inorganic mercury were still appropriate. In line with JECFA, the CONTAM Panel established tolerable weekly intake values of 4 and 1.3 $\mu\text{g kg}^{-1}$ bw for inorganic mercury and for methylmercury, respectively, [91].

13.4.5 Manganese (Mn)

Manganese (Mn) is one of the most abundant and widely distributed metals in nature. In fact, it is typically found in rocks, soils, and waters. The Earth's crust consists of 0.1% of Mn. As a constituent of the soil, its concentrations range from 40 to 900 mg kg^{-1} . Pure Mn does not occur in the environment.

Living organisms require Mn only in trace amounts. It is a constituent of metallo-enzymes and acts as an enzyme activator. Moreover, it plays essential roles in many metabolic and non-metabolic regulatory functions, such as:

- Bone mineralization
- Connective tissue formation
- Energetic metabolism
- Enzyme activation
- Immunological and nervous system activities
- Reproductive hormone regulation
- Cell defence
- Amino acid, lipid, protein, and carbohydrate metabolisms
- Glycosaminoglycans formation
- Blood clotting [92].

Manganese is considered an emerging contaminant because it is not just a perceived but a real threat to the human health and the environment. In the

5 IMERC Fact Sheet – Mercury Use in Thermostats. <http://www.newmoa.org/prevention/mercury/imerc/factsheets/thermostats.cfm>. 2010.

6 Indoor Air Mercury. <http://www.newmoa.org/prevention/mercury/mercuryindoor.pdf>. 2003.

last century, the massive production of manganese-containing compounds⁷ has attracted the attention of scientists who investigated Mn as a potential emerging contaminant in the environment, especially in the marine environment [93]. Natural waters, such as lakes, streams, rivers, and oceans, contain variable quantities of dissolved Mn, ranging from 10 to 10,000 $\mu\text{g L}^{-1}$. In water, most Mn compounds tend to attach to circulating particles or settle as sediment. Mn exists in the aquatic environment in two main forms: Mn_2^+ and Mn_4^+ . Switching between these two forms occurs *via* redox reactions that may be abiotic or biotic [94]. Ocean spray, forest fires, vegetation, crustal rock, and volcanic activity are the major natural atmospheric sources of Mn.

In humans, Mn excess is associated with a characteristic syndrome called “manganese madness” or “Parkinson-like” diseases [95]. This neurodegenerative disorder is due to the accumulation of Mn inside intracellular compartments.

13.4.6 Antimony (Sb)

The presence of antimony in the Earth’s crust is estimated to be 0.2 to 0.5 ppm, and it is found in more than 100 mineral species. Sb is sometimes found natively, but more frequently it is found in sulfide stibnite (Sb_2S_3) which is the predominant ore mineral. In 2015, according to the US Geological Survey, China accounted for 76.7% of total antimony production, followed in the second place by Russia with 6.0%, and Australia with 3.7%. [96]

About 60% of antimony is used in flame retardants and 20% in alloys for batteries, plain bearings, and solders [97]. The effects of antimony and its compounds on human and environmental health differ widely. The elemental antimony metal does not affect human and environmental health. Inhalation of antimony trioxide is considered harmful and suspected of causing cancer.

Because it can have both acute and chronic toxicity effects, Sb is regulated in drinking water in the United States, Canada, Europe, and Japan at action levels ranging between 2 and 6 $\mu\text{g L}^{-1}$. It has been shown that antimony, can also leach from PET plastic water bottles, producing the highest levels of human exposure to antimony, up to $\approx 10 \mu\text{g L}^{-1}$ [98]. Antimony trioxide (Sb_2O_3) is used as a catalyst in the manufacture of PET plastics, which can contain $>100 \text{ mg kg}^{-1}$ of antimony. This is a concern because of the growing popularity of bottled water. PET bottles have been used for the last four decades and have gradually replaced PVC and glass bottles. Bach *et al.* [99] published a comprehensive review of chemicals found in PET bottled water and their toxicological assessment, where antimony, formaldehyde, and acetaldehyde were noted as clearly migrating from the PET plastic into the water.

13.4.7 Technology-Critical Elements

Although considerable progress has been made in understanding the environmental fate and ecotoxicological behavior of the more traditionally used elements, the use of a further range of trace elements, whose properties are required for use in an ever expanding list of new technologies, is rapidly

⁷ Metallurgic and chemical products, municipal wastewater discharges, sewage sludge, alloys, steel, iron, ceramics, fungicide products.

increasing. These elements, which include Ga, Ge, In, Te, Nb, Ta, Tl, the Pt group elements, and most of the rare-earth elements are now essential components in a variety of applications ranging from information and telecommunication technology, semiconductors, electronic displays and optic/photonic to “green energy” technologies. Their current strategic importance is such that they have now been labeled as “energy-critical elements” or “technology-critical elements.” Due to their high economic relevance and the dependency of the EU on imports, the EU has identified 14 critical materials for which, at the moment, no mining zones with an acceptable short- to mid-term profit exist within the EU borders. These critical materials identified by the EU encompass most of the technology-critical elements mentioned above.

13.4.8 Radionuclides

All chemical elements have radionuclides. A radionuclide (radioactive nuclide, radioisotope, or radioactive isotope) is an atom that has excess nuclear energy, making it unstable. This excess energy can be emitted from the nucleus as gamma radiation, or create and emit a new particle (alpha particle or beta particle) from the nucleus, or transfer this excess energy to one of its electrons, causing that electron to be ejected as a conversion electron. During such processes, the radionuclide is said to undergo radioactive decay. These emissions constitute ionizing radiation.

Radionuclides are used in two major ways: either for their radiation alone (irradiation, nuclear batteries) or for the combination of chemical properties and their radiation (tracers, biopharmaceuticals). Table 13.2 shows physical and biological half-lives of main radionuclides.

13.5 Biotoxins

Toxins⁸ are small molecules, peptides, or proteins that are capable of causing disease on contact with or absorption by body tissues interacting with enzymes

Table 13.2 Physical and biological half-lives of several radionuclides.^{a)}

Element	Half-life ^{b)}		Ray type	Element	Half-life ^{b)}		Ray type
	Physical	Biological			Physical	Biological	
³ H	12.3 y	19 d	β^-	¹³⁷ Cs	30.2 y	70 d	β^-, γ
¹⁴ C	5730 y	35 d	β^-	¹⁴⁰ Ba	12.8 d	200 d	β^-, γ
³² P	14.3 d	10 y	β^-	²²² Rn	3.8 d		α
⁴⁰ K	1.28×10^9 y	37 d	β^-, β^+	²²⁶ Ra	1600 y	55 d	α, γ
⁴⁵ Ca	165 d	50 y	β^-, γ	²³³ U	1.62×10^5 y	300 d	α, γ
⁹⁰ Sr	28.1 d	11 y	β^-	²³⁹ Pu	2.44×10^4 y	120 y	α, γ
¹³¹ I	8.1 d	138 d	β^-, γ				

a) Data taken from Ref. [58].

b) d: days; y: years.

⁸ See Glossary.

or cellular receptors. Toxins from mold fungi and bacteria are among the oldest forms of contamination for foodstuffs.

According to an International Committee of the Red Cross review of the Biological Weapons Convention:

“Toxins are poisonous products of organisms; unlike biological agents, they are inanimate and not capable of reproducing themselves,” and “Since the signing of the Convention, there have been no disputes among the parties regarding the definition of biological agents or toxins.”

According to title 18 of the U.S. code:

“... the term “toxin” means the toxic material or product of plants, animals, microorganisms,⁹ or infectious substances, or a recombinant or synthesized molecule, whatever their origin and method of production ...”

13.5.1 Mycotoxins

Many species of mold fungi produce toxins; they are subsumed under the name, mycotoxins. Mycotoxins are naturally occurring toxic secondary metabolites of fungal species (e.g., *Aspergillus* spp., *Fusarium* spp., and *Penicillium* spp.) that can grow on a wide variety of crops including wheat (*Triticum* spp.) and corn (*Zea mays*) [100, 101].

Table 13.3 lists some of the toxic mold fungi, including the foods they prefer to attack. While extensive research has been conducted on the production of mycotoxins and their occurrence in agricultural products such as food and feed [102, 103], little has been done to determine their environmental fate and distribution [104–106]. Several studies have documented mycotoxins as potentially important, but under investigated, environmental contaminants [104, 107–110].

Table 13.3 Mold fungi that form mycotoxins, and their main substrates.^{a)}

Mold fungus	Toxin	Main substrates
<i>Aspergillus flavus</i> and others	Aflatoxin	Bread, fruit, peanuts, cheese, meat, etc.
<i>Aspergillus ochraceus</i>	Ochratoxin A	Bread
<i>Aspergillus versicolor</i>	Sterigmatocystin	Grain, pod-produce
<i>Byssoschlamys fulva</i>	Byssoschlamine acid	Fruit juices
<i>Penicillium citrinum</i>	Citrinin acid	Rice
<i>Penicillium urticae</i>	Patulin	Malt
<i>Penicillium rubrum</i>	Rubratoxin	Grain

a) Data taken from Ref. [58].

⁹ Including, but not limited to, bacteria, viruses, fungi, rickettsiae, or protozoa.

Potential environmental pathways include the release from infected plants, manure from exposed livestock, and human waste *via* WWTP. The presence of mycotoxins has been documented in tile drains, streams and municipal effluent providing evidence of both diffuse and point sources of mycotoxins to the environment [110].

Mycotoxins can exhibit a broad range of effects including carcinogenicity, neurotoxicity, and developmental toxicity [111]. The presence of mycotoxins lowers the quality of food and feedstuffs by deteriorating the nutritional content and potentially affecting animal health [112]. While the number of potential toxic metabolites of fungi has been estimated to be in thousands, only several hundred have been identified to date [113].

Aflatoxin was discovered in 1960 in a sensational manner (100,000 turkeys and other domestic fowls became the victims of this mycotoxin when they were fed at a facility that was contaminated with *Aspergillus flavus*). At least 14 types of aflatoxin occur in nature (see Figure 13.4). Aflatoxin B₁ proved to be the most toxic of the aflatoxins, having an LD_{50} value of $17.9 \mu\text{g kg}^{-1}$ (see Table 13.4). Aflatoxins can combine with proteins and they can accumulate in foods that undergo protein enrichment. Fungi that attack cultured plants are generally less consequential for human health.

13.5.2 Algal Toxins

Algal toxins of increasing interest are extremely potent neurotoxins or hepatotoxins that are produced from dinoflagellates, diatoms, or cyanobacteria.¹⁰ Drinking water can be contaminated by the toxins of certain algae called phytoplankton toxins. The necessary conditions for such a contamination is the presence of algae in water that serves as the source of drinking water.

Increased discharges of nutrients (from agricultural runoff and wastewater discharges) have led to increased algal blooms and an accompanying increased incidence of shellfish poisoning, large fish kills, and deaths of livestock and wildlife as well as illness and death in humans. Toxins produced by these algae have been implicated in the adverse effects that are caused. These toxins can directly affect humans (by drinking contaminated water) or indirectly (by eating contaminated aquatic animals that have fed on the algae).

Various species of algae are capable of forming phytoplankton toxins (see Figure 13.5 and Table 13.5). The most commonly occurring algal toxins are microcystins, nodularins, anatoxins, cylindrospermopsin, and saxitoxins. “Red tide” toxins are also often found in coastal waters.

Currently, in the EU, the maximum permitted levels (MPL) have been set for six groups of marine toxins in shellfish: Domoic acid group (DA, MPL: 20 mg kg^{-1}) as amnesic shellfish poisoning (ASP) toxins, Saxitoxin group (STX, MPL: 800 mg kg^{-1}) as paralytic shellfish poisoning (PSP) toxins, Okadaic acid (OA, MPL: 160 mg kg^{-1}) group, Pectenotoxin (PTX, MPL: 160 mg kg^{-1}) group, Yessotoxin (YTX, MPL: 3750 mg kg^{-1}) group, and Azaspiracid (AZA, MPL: 160 mg kg^{-1}) group, all belonging to the lipophilic toxin group [114].

¹⁰ Mostly cyanobacterial toxins produced from blue-green algae.

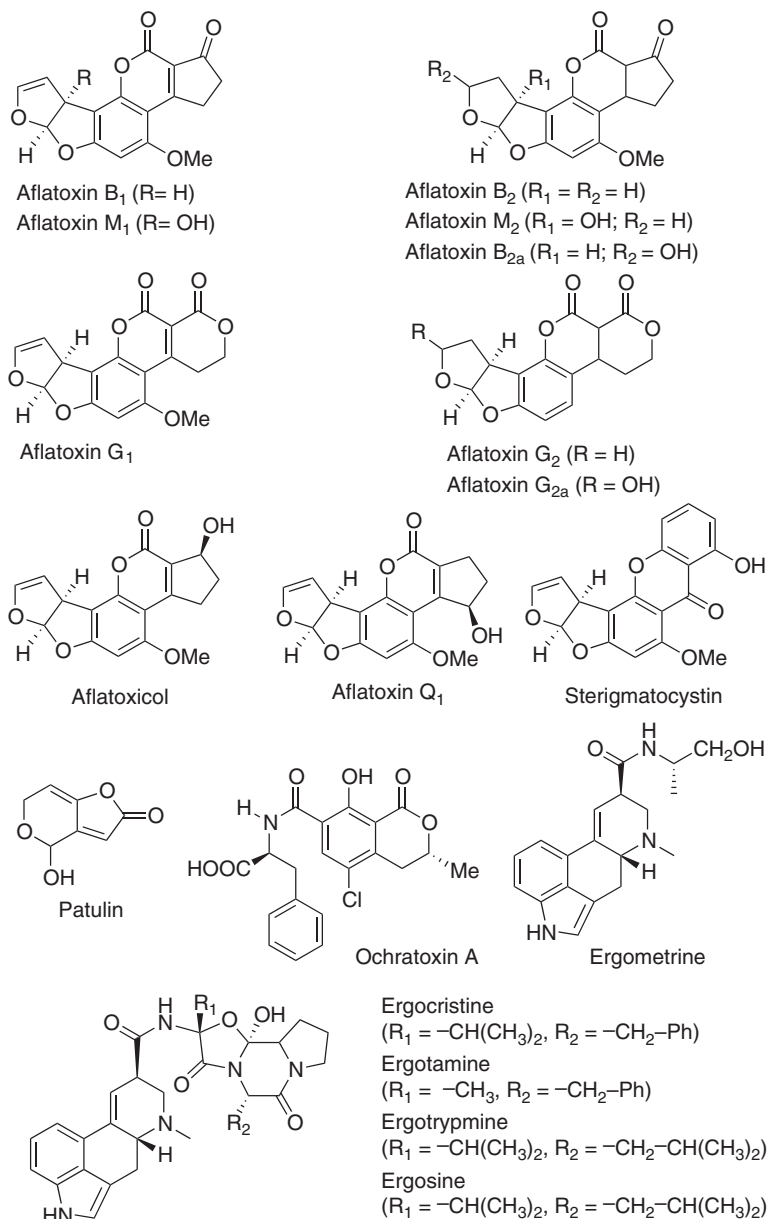


Figure 13.4 Structure of some mycotoxins, including ergot alkaloids.

Merel *et al.* [115] reviewed the occurrence and management of harmful cyanobacterial blooms and their toxins in surface water and drinking water, while Kaushik and Balasubramanian [116] summarized the methods and approaches for detecting cyanotoxins in environmental samples. Several new methods have been developed for algal toxins. Lemoine reported a new method

Table 13.4 Content ($\mu\text{g kg}^{-1}$) of aflatoxin B₁ in some foods with mold.^{a)}

Food	Mold fungus	Aflatoxin B ₁
Fruit loaf	<i>Aspergillus glaucus</i>	100
Peanuts	<i>Aspergillus flavus</i>	1100
Walnuts	<i>Aspergillus flavus</i>	20
Oranges	<i>Penicillium expansum</i>	
	<i>Penicillium citromyces</i>	5–50
Lemons	<i>Penicillium digitatum</i>	20–30
Pears	<i>Aspergillus niger</i>	5
Bacon	<i>Aspergillus flavus</i>	1000–5000
Tomato pulp	<i>Aspergillus flavus</i>	20
Bread (white)	<i>Penicillium glaucum</i>	20
Bread (whole grain)	<i>Aspergillus glaucus</i>	10

a) Data taken from Ref. [58].

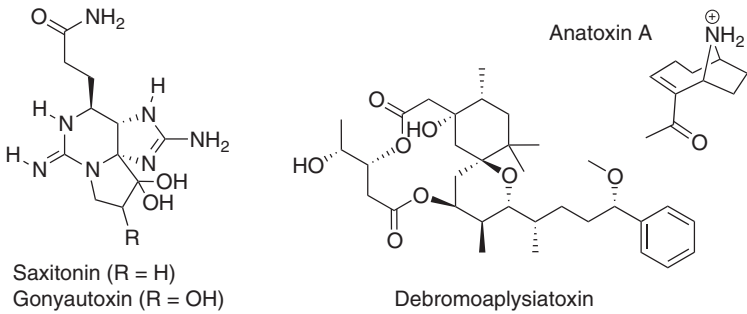


Figure 13.5 Structure of some phytoplankton toxins.

Table 13.5 Key phytoplankton toxins and their occurrence.

Species	Toxins	Occurrence
Cyanophyceae		
<i>Microcystis aeruginosa</i>	Microcystin	Fresh water
<i>Anabaena flos-aquae</i>	Anatoxin A	Fresh water
<i>Aphanizomenon flos-aquae</i>	Saxitonin	Fresh water
<i>Lyngbya gracilis</i>	dibromo-aplysiatoxin	Sea water
Dinophyceae		
<i>Gonyaulax catenella</i>	Saxitonin	Sea water
<i>Gonyaulax tamarensis</i>	Saxitonin, Gonyautoxin	Sea water
<i>Gambierdiscus toxicus</i>	Ciguateratoxin	Sea water
Haptophyceae		
<i>Prymnesium parvum</i>	Prymnesin	Brackish water

for anatoxin-A using laser-diode thermal desorption-APCI-MS/MS [117]. Also, Zamyadi *et al.* [118] published a study of cyanobacterial and microcystin accumulation in a DWTP.

13.5.3 Other Marine Toxins

13.5.3.1 Cyclic Imines

Spirolides, gymnodimines, pinnatoxins, and pteriatoxins are marine toxins, present in shellfish and are produced by dinoflagellates [119, 120]. They are grouped together due to similarities in their chemical structure (imino group as their common pharmacophore) and toxicity in mice [119]. In Europe, Spirolides have been detected in a number of countries, while gymnodimines have been reported in shellfish from Croatia [121–123]. Gymnodimines have a global distribution, being found in shellfish from Tunisia [124] to New Zealand [125]. Pinnatoxins were also identified in shellfish in Europe [126].

13.5.3.2 Ciguatoxins

Ciguatoxins, which accumulate mainly in tropical and subtropical fish, are lipid-soluble polyether compounds produced by dinoflagellates from the genus *Gambierdiscus* spp. [127]. This family of toxins causes ciguatera fish poisoning which is linked to a wide variety of gastrointestinal, neurological, and cardiovascular symptoms, depending on the particular variety of the toxin. During the last 10 years, ciguatoxins have been identified for the first time in fish (*Seriola* spp.) caught in European waters of Canary Islands [128] and the microalgae *Gambierdiscus* spp. have also been described in the Mediterranean Sea [129]. The USFDA has proposed guidance levels of $<0.1 \mu\text{g kg}^{-1}$ C-CTX-1 equivalents and $<0.01 \mu\text{g kg}^{-1}$ P-CTX-1 equivalents [127].

13.5.3.3 Azaspiracids (AZAs)

AZAs are nitrogen-containing polyether compounds that have a chemical structure consisting of a spiral ring that contains a heterocyclic amine and an aliphatic carboxylic acid moiety [130]. Incidents of shellfish poisoning in humans have particularly occurred in Northern Europe. New AZAs, AZA metabolites, and conversion products result during cooking, all with unknown toxicity and occurrence. These are included in the group of emerging marine toxins [130].

13.5.3.4 Tetrodotoxin (TTX)

Consisting of a positively charged guanidine group and a pyrimidine ring with six hydroxyl groups, this toxin has been isolated from several species of puffer fish (*Tetraodontidae* family). However, studies have also revealed its wide distribution in both terrestrial and marine animals. [120, 131] Tetrodotoxin is a neurotoxin, specifically blocking voltage-gated sodium channels of nerve fibers. Toxicity can lead to weakness or paralysis and even death [132]. Neither TTX nor its analogs are regulated by European legislation.

13.5.3.5 Palitoxins

Palytoxin-group toxins are complex polyhydroxylated compounds with both lipophilic and hydrophilic areas in their chemical structure. They have been detected mainly in marine zoanthids (soft corals) of the genus *Palythoa* and dinoflagellates of the genus *Ostreopsis*. Blooms of *Ostreopsis* spp. have recently been reported in several European countries. This occurrence may result in contamination of shellfish species intended for human consumption [133–136]. EFSA has proposed a maximum permitted level of 250 $\mu\text{g kg}^{-1}$ shellfish [135].

13.5.4 Bacterial Toxins

In addition to mycotoxins and phytoplankton toxins, bacterial toxins can also affect food. The toxin given off by *Clostridium botulinum* is among the most dangerous. These bacteria produce a toxic protein that attacks the nervous system, and can cause death in 1–2 days. Salmonella, a group of enterobacteria, can attack meat, fish, and so on. If they are not handled or stored hygienically, they can produce typhus and paratyphoid. The most frequent form of bacterial toxins derives from *Staphylococcus aureus*. Only 0.5–1 μg of the proteic toxin can cause toxic effects (diarrhea and body ache).

13.5.5 Naturally Occurring Toxins in Vegetable Foodstuffs

A number of food plants themselves generate toxins (see Figure 13.6). For example, green beans contain proteins that produce toxins that cause bloody diarrhea and cramps. Legumes contain lectins or phytohemag – glutinins, proteins that cause erythrocytes to agglutinate. Plants often produce trypsin inhibitors. Legumes, sweet potatoes, potatoes, and red beets produce toxins that inhibit the decomposition of proteins. Other plants contain saponins, glycosides that tend to produce foam in watery solutions. In some cases, they can cause hemolysis. Cabbage contains glucobrassicin, thioglycoside that releases thiocyanate by enzymatic reduction, and inhibits the formation of thyroxine.

13.6 Microorganisms

Outbreaks of waterborne diseases in the United States and other parts of the world have necessitated improved analytical methods for detecting and identifying microorganisms in water and other environmental samples. Several microorganisms (bacteria, virus, and protozoa) are included on the CCL-4.¹¹ New methods have been developed for detection of microorganisms. For example, Aw and Rose [137] reviewed the molecular tools for rapid, high-throughput, sensitive, and specific detection of a wide spectrum of pathogens.

¹¹ <https://www.epa.gov/ccl/microbial-contaminants-ccl-4>.

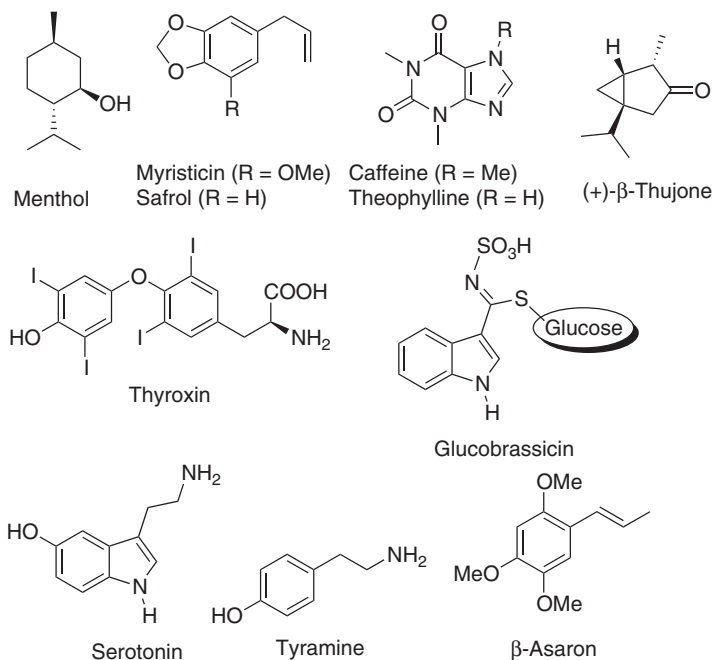


Figure 13.6 Structure of some toxins in vegetable foodstuffs.

13.7 Contaminants on the Horizon: Ionic Liquids and Prions

Ionic liquids are organic salts with a low melting point ($<100\text{ }^{\circ}\text{C}$) that are being promoted as “green chemistry” replacements to traditional solvents used in industry [98]. They are currently one of the hottest areas in chemistry, with many papers and reviews highlighting ionic liquids as a state-of-the-art innovative approach to sustainable chemistry, due to their low vapor pressures and flammability. Ionic liquids have unique properties, including tunable viscosity, miscibility, and electrolytic conductivity, which make them useful for many applications, including organic synthesis and catalysis, production of fuel cells, batteries, coatings, oils, and nanoparticles, as well as other chemical-engineering and biotechnology applications. Their chemical structures typically involve a cationic or anionic polar headgroup with accompanying alkyl side chains. Cationic head groups include imidazolium, pyridinium, pyrrolidinium, morpholinium, piperidium, quinolinium, quaternary ammonium, and quaternary phosphonium moieties; anionic head groups include tetrafluoroborate BF_4^- , hexafluorophosphate (PF_6^-), bis(trifluoromethylsulfonyl)-imide $[(\text{CF}_3\text{SO}_2)_2\text{N}^-]$, dicyanamide $[(\text{CN})_2\text{N}^-]$, chloride, and bromide [98]. Current data show that ionic liquids are toxic in nature and that their toxicities vary considerably across organisms and trophic levels [98]. The introduction of polar groups to the alkyl chains has been shown to decrease their toxicity and increase biodegradation.

Prions are infectious particles composed of a protein in a misfolded form. Like viruses, they are not living organisms, but they can cause fatal neurodegenerative diseases, such as bovine spongiform encephalopathy in cattle (“mad cow disease”), chronic wasting disease in deer, and Creutzfeldt-Jakob disease and kuru in humans. Prions are highly resistant to degradation and to disinfection and can persist in soil for years. As a result, entry to the environment may not occur through discharge to surface water but could occur through application of biosolids to agricultural land.

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A

InChI Key for the Most Relevant Compounds in this Book

Acetaminophen: RZVAJINKPMORJF-UHFFFAOYSA-N
2-Aminobenzimidazole: JWYUFVNJZUSCSM-UHFFFAOYSA-N
Amlodipine: HTIQEAQVCYTUBX-UHFFFAOYSA-N
Amoxicillin: LSQZJLSUYDQPKJ-NJBDSQKTS-A-N
Amphetamine: KWTSDXURSMDCE-UHFFFAOYSA-N
Ampicillin: AVKUERGKIZMTKX-NJBDSQKTS-A-N
Antipyrine: VEQOALNAAJBPNY-UHFFFAOYSA-N
Aspirin: BSYNRYMUTXBXSQ-UHFFFAOYSA-N
Atenolol: METKIMKYRPLGS-UHFFFAOYSA-N
Atorvastatin: XUKUURHRXDUEBC-KAYWLYCHSA-N
Azithromycin: MQTOSJVFJKJCRP-BICOPXKESA-N
Benzo[*a*]pyrene: FMMWHPNWAFZXNH-UHFFFAOYSA-N
Benzoilecgonina: GVGYEFKIHJTNQZ-RFQIPJPSA-N
Benzophenone-3: DXGLGDHPHMLXJC-UHFFFAOYSA-N
Benzophenone-4: CXVGEDCSTKKODG-UHFFFAOYSA-N
Benzophenone: RWCCWEUUXYIKHB-UHFFFAOYSA-N
1*H*-Benzotriazole: QRUDEWIWKLJBPS-UHFFFAOYSA-N
2-Benzyl-4-chlorophenol: NCKMMSIFQUPKCK-UHFFFAOYSA-N
Benzylpenicillin: JGSARLDLIJGVTE-MBNYWOFBSA-N
Bezafibrate: IIBYAHWJQTYFKB-UHFFFAOYSA-N
2-Benzothiazolesulfonic acid: ZCXGMSGCBDSOY-UHFFFAOYSA-N
Bisoprolol: VHYCDWMUTMEGQY-UHFFFAOYSA-N
Bisphenol A: IISBACLAFLKSPIT-UHFFFAOYSA-N
Bromazepam: VMIYHDSEFNYSJL-UHFFFAOYSA-N
***tert*-Butyl methyl ether:** BZLVMXJERCZMT-UHFFFAOYSA-N
2,6-di-*tert*-Butylphenol: DKCPKDPYUFEZCP-UHFFFAOYSA-N
Caffeine: RYYVLZVUVIJVGH-UHFFFAOYSA-N
Cannabinol: VBGLYOIFKLUMQG-UHFFFAOYSA-N
Carazolol: BQXQGZPYHWWCEB-UHFFFAOYSA-N
Carbamazepine: FFGPTBGBLSHEPO-UHFFFAOYSA-N
Cefalexin: ZAIPMKNFIOOWCQ-UEKVPHQBSA-N
Cephalexin: ZAIPMKNFIOOWCQ-UEKVPHQBSA-N

Chloroacetaldehyde: QSKPIOLLLBIHNAC-UHFFFAOYSA-N
Chloropicrin: LFHISGNCFUNFFM-UHFFFAOYSA-N
Cholesterol: HVYWMOMLDIMFJA-DPAQBDIFSA-N
Chrysene: WDECIBYCCFPHNR-UHFFFAOYSA-N
Cilazapril: HHHKFGXWKKUNCY-FHWLQOOXSA-N
Ciprofloxacin: MYSWGUAQZAJOK-UHFFFAOYSA-N
Citalopram: WSEQXVZVJXJVFP-UHFFFAOYSA-N
Clarithromycin: AGOYDEPGAOXOCK-KCBOHYOISA-N
Clofibric acid: TXCGAZHTZHNUAI-UHFFFAOYSA-N
Cocaine: ZPUCINDJBIVPJ-LJISPDSOSA-N
Codeine: OROGSEYTTFOCAN-DNJOTXNNSA-N
Coprostanol: QYIXCDOBOSTCEI-NWKZBHTNSA-N
Cybutryne: HDHLIWCXDDZUFH-UHFFFAOYSA-N
Decamethylcyclopentasiloxane: XMSXQFUHVWRWGNA-UHFFFAOYSA-N
Decamethyltetrasiloxane: YFCGDEUVHLPRCZ-UHFFFAOYSA-N
Derquantel: DYVLXWPZFQQUIU-WGNDVSEMSA-N
Dexamethasone: UREBDLICKHMuKA-CXSFZGCWSA-N
Diatrizoic acid: YVPYQUNUQOZFHG-UHFFFAOYSA-N
Diazepam: AAOVKJBEBIDNHE-UHFFFAOYSA-N
2,4-Dinitrophenol: UFBJCMHMOXMLKC-UHFFFAOYSA-N
Dibutyltin: AYOHILKLSOJJQH-UHFFFAOYSA-N
Diclofenac: DCOPUUMXTXDBNB-UHFFFAOYSA-N
N,N-Diethyl-m-tolamide: MMOXZBCLCQITDF-UHFFFAOYSA-N
N,N-Diethyl-3-methylbenzamide: MMOXZBCLCQITDF-UHFFFAOYSA-N
Diethylstilbestrol: RGLYKWWBQGJZGM-ISLYRVAYSA-N
Dihydrocodeine: RBOXVHNMFORY-DNJOTXNNSA-N
Dihydrotestosterone: NVKAWKQGWWIWPM-ABEVXSGRSA-N
Dimethyl fumarate: LDCRTTXIJACKKU-ONEGZZNNSA-N
Diethyl phthalate: MQIUGAXCHLFZKX-UHFFFAOYSA-N
Diphenhydramine: ZZVUWRFHKOJYTH-UHFFFAOYSA-N
Dipyrene: DJGAAPFSPWAYTJ-UHFFFAOYSA-M
Dodecamethylcyclohexasiloxane: IUMSDRXLFWAGNT-UHFFFAOYSA-N
Dodecamethylpentasiloxane: FBZANXDWQAVSTQ-UHFFFAOYSA-N
Doxycycline: SGKRLCUYIXIAHR-AKNGSSGZSA-N
Emamectin: CXEGAUYXQAKHKJ-NSBHKLITSA-N
Enalapril: GBXSMTUPTTWBMN-XIRDDKMYSA-N
Ephedrine: KWGRBVOPPLSCSI-WPRPVWTQSA-N
Erythromycin: ULGZDMOVFRHVEP-RWJQBGPGSA-N
17 β -Estradiol: VOXZDWNVPVJITMN-ZBRFXRBCSA-N
Estriol: PROQIPRRNZUXQM-ZXXIGWHRSA-N
Estrone: DNXHEGUUPJUMQT-CBZIJGRNSA-N
Ethylparaben: NUVBSKCKDOMJSU-UHFFFAOYSA-N
Fenofibric acid: MQOBSOSZFYZQOK-UHFFFAOYSA-N
Fenoprofen: RDJGLLICXDHJDY-UHFFFAOYSA-N
Flumequine: DPSPPIUMHPXMA-UHFFFAOYSA-N
Flunitrazepam: PPTYJKAXVCCBDU-UHFFFAOYSA-N
Fluoranthene: GVEPBHOBDDJJI-UHFFFAOYSA-N

Fluoxetine: RTHCYVBBDHJXIQ-UHFFFAOYSA-N
Furosemide: ZZUFCTLCJUWOSV-UHFFFAOYSA-N
Galaxolide: ONKNPOPIGWHAQC-UHFFFAOYSA-N
Gemfibrozil: HEMJJKBWTPKOJG-UHFFFAOYSA-N
Heroin: GVGLGOZIDCSQPN-PVHGPHFFSA-N
1,2,5,6,9,10-Hexabromocyclododecane: DEIGXXQKDWULML-UHFFFAOYSA-N
Hexamethylcyclotrisiloxane: HTDJPCNNEPUOOQ-UHFFFAOYSA-N
Hydrochlorothiazide: JZUFKLXOESDKRF-UHFFFAOYSA-N
 γ -Hydroxybutyric acid: SJZRECIVHVDYJC-UHFFFAOYSA-N
Ibuprofen: HEFNNWSXXWATRW-UHFFFAOYSA-N
Indomethacine: CGIGDMFJXJATDK-UHFFFAOYSA-N
Iopromide: DGAIEPBNLOQYER-UHFFFAOYSA-N
Iothalamic acid: UXIGWFXRQKWHHA-UHFFFAOYSA-N
Irbesartan: YOSHYTLCDANDAN-UHFFFAOYSA-N
Ketamine: YQEZLKZALYSWHR-UHFFFAOYSA-N
Ketoprofen: DKYWVDODHFEZIM-UHFFFAOYSA-N
Levamisole: HLFSDGLLUJUHTESNVBAGLBSA-N
Levonorgestrel: WWYNJERNGUHSAO-XUDSTZEESA-N
Lincomycin: OJMMVQQUTAEWLP-KIDUDLJLSA-N
Lorazepam: DIWRORZWFOCLC-UHFFFAOYSA-N
Losartan: PSIFNNKUMBCKDQ-UHFFFAOYSA-N
Lysergic acid diethylamide: VAYOSLLFUXYJDT-RDTXWAMCSA-N
Melengestrol acetate: UDKABVSQKJNZBH-DWNQPYOZSA-N
Meloxicam: ZRVUJXDFFKFLMG-UHFFFAOYSA-N
Meprobamate: NPPQSCRMBWNHMMW-UHFFFAOYSA-N
Mescaline: RHCSKNNOAZULRK-UHFFFAOYSA-N
Metformin: XZWYZXLIPXDOLR-UHFFFAOYSA-N
Methamphetamine: MYWUZJCMWCOHBA-VIFPVBQESA-N
3-(4-Methylbenzylidene)camphor:
 HEOCBCNFKCOKBX-KAMYIIQDSA-N
3,4-Methylenedioxy-N-ethylamphetamine:
 PVXVWWANJJIWJOO-UHFFFAOYSA-N
3,4-Methylenedioxyamphetamine:
 NGBBVGWCFBOGO-UHFFFAOYSA-N
3,4-Methylenedioxymethamphetamine:
 SHXWCYVOXRDMCX-UHFFFAOYSA-N
Methylparaben: LXCFLQKKLGQFO-UHFFFAOYSA-N
Metoprolol: IUBSYMUCCVWXPE-UHFFFAOYSA-N
Microcystin-LR: ZYZCGGRZINLQBL-GWRQVWKTSA-N
Morphine: BQJCRHHNABKAKU-KBQPJGBKSA-N
Nadolol: VWPOSFSPZNDTMJ-UCWKZMIHSA-N
Naphthalene: UFWIBTONFRDIAS-UHFFFAOYSA-N
Naproxen: CMWTZPSULFXXJA-VIFPVBQESA-N
Nicotine: SNICXCGAKADSCV-JTQLQIEISA-N
Nitroglycerin: SNIOPGDIGTZGOP-UHFFFAOYSA-N
Nitrosodimethylamine: UMFJAHHVKNCGLG-UHFFFAOYSA-N

4-Nonylphenol: IGFHQFPISBGKE-UHFFFAOYSA-N
2-[2-(4-Nonylphenoxy)ethoxy]ethanol:
 BLXVTZPGEOGTGG-UHFFFAOYSA-N
Octamethylcyclotetrasiloxane: HMMGMWAXVFQUOA-UHFFFAOYSA-N
Octamethyltrisiloxane: CXQXSVUQTKDNFP-UHFFFAOYSA-N
2-(2-(4-Octylphenoxy)ethoxy)ethanol:
 NMTRTIUWHYPKTQ-UHFFFAOYSA-N
Ofloxacin: GSDSWSVVBLHKDQ-UHFFFAOYSA-N
Omeprazole: SUBDBMMJDZJVOS-UHFFFAOYSA-N
Oxytetracycline: OWFJMIVZYSULZ-PXOLEDIWSA-N
Paroxetine: AHOUBRZNHFOSL-YOEHRQHSAN
Perfluorooctanoic acid: SNGREZUHAYWORS-UHFFFAOYSA-N
Perfluorooctanesulfonic acid: YFSUTJLHUFNCNZ-UHFFFAOYSA-N
Phenazone: VEQOALNAAJBPNY-UHFFFAOYSA-N
Phencyclidine: JTJMJGYZQZDUJJ-UHFFFAOYSA-N
Phenytoin: CXOFVDLJLONNDW-UHFFFAOYSA-N
Piroxicam: QYSPLQLAKJAUT-UHFFFAOYSA-N
Progesterone: RJKFOVLPORLFTN-LEKSSAKUSA-N
Propranolol: AQHHHDLHHXJYJD-UHFFFAOYSA-N
Propylparaben: QELSKZZBTMNZEB-UHFFFAOYSA-N
Pseudoephedrine: KWGRBVOPPLSCSI-WCBMZHEXSA-N
Psilocybine: QVDSEJDULKHLHCG-UHFFFAOYSA-N
Ranitidine: VMXUWOKSQNHOCAN-UKTHLTGXSA-N
Salicylic acid: YGSDEFMJLZEOE-UHFFFAOYSA-N
Simvastatin: RYMZZMVNJRMUDD-HGQWONQESA-N
Sodium lauryl sulfate: DBMJMQXJHONAFJ-UHFFFAOYSA-M
Sucralose: BAQAVOSOZGMPRM-QBMZZYIRSA-N
Sulfadiazine: SEEPANYCNGTZFQ-UHFFFAOYSA-N
Sulfamethizole: VACCAVUAMIDAGB-UHFFFAOYSA-N
Sulfamethoxazole: JLKIGFTWXXRPMT-UHFFFAOYSA-N
Tenoxicam: LZNWYQJJBLYLT-UHFFFAOYSA-N
Testosterone: MUMGGGOZAMZWBJJ-DYKIIFRCSAN
Tetrabromobisphenol A: VEORPZCZECFIRK-UHFFFAOYSA-N
Tetracycline: NWXMGUDVXFXRIG-WESIUVDSAN
Tetradecamethylhexasiloxane: ADANNTOYRVPQLJ-UHFFFAOYSA-N
2,4,7,9-Tetramethyl-5-decyne-4,7-diol:
 LXOFYPKXCSULTL-UHFFFAOYSA-N
Thiabendazole: WJCNZQLZVWNLKY-UHFFFAOYSA-N
Thiacloprid: HOKKPVIRMDYBPB-UVTDQMKNSAN
Tilmicosin: JTSDBFGMPLKDCD-XVFHVFLVSA-N
Timolol: BLJRMJGRPQVNF-JTQLQIEISAN
Trazodone: PHLBKPHSAVXXEF-UHFFFAOYSA-N
Triacetin: URAYPUMNDPQOKB-UHFFFAOYSA-N
2,2,2-Trichloroacetamide: UPQQXPKAYZYUKO-UHFFFAOYSA-N
Triclabendazole: NQPDXQQCQDHHW-UHFFFAOYSA-N
Triclosan: XEQQLINVKFYRCS-UHFFFAOYSA-N
Trimethoprim: IEDVJHCEMCRBQM-UHFFFAOYSA-N

Tris(2-chloroethyl) phosphate: HQUQLFOMPYWACS-UHFFFAOYSA-N

Tylosin: WBPYTXDJUQJLPQ-VMXQISHHSA-N

Valsartan: AYFQOWOITXDUOI-MTFPVJPISA-N

Venlafaxine: PNVNVHUZROJLTJ-UHFFFAOYSA-N

Warfarin: PJVWKTQMONHTI-UHFFFAOYSA-N

Xylazine: BPICBUSOMSTKRF-UHFFFAOYSA-N

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